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⑤⑤ **Renin inhibitors, processes for preparing them, methods for using them, and compositions containing them.**

⑤⑦ The invention concerns novel renin-inhibitory peptides which are useful for treating renin-associated hypertension, congestive heart failure, and hyperaldosteronism. Processes for preparing the peptides, novel intermediates useful in the preparation thereof, compositions containing them, and methods of using them are included. Also included is a diagnostic method which uses the compounds to determine the presence of renin-associated hypertension, congestive heart failure, or hyperaldosteronism.

EP 0 314 060 A2

RENIN INHIBITORS, PROCESSES FOR PREPARING THEM, METHODS FOR USING THEM, AND COMPOSITIONS CONTAINING THEM

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of United States Application Serial No. 113,772 filed October 26, 1987.

BACKGROUND OF THE INVENTION

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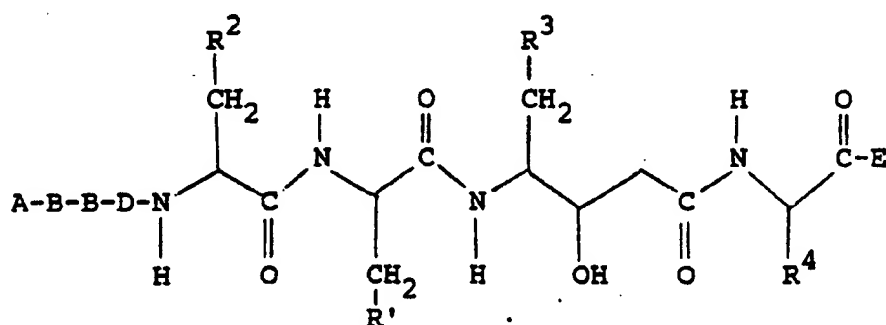
Renin is a natural enzyme which is released into the blood from the kidney. It cleaves its natural substrate, angiotensinogen, releasing decapeptide, angiotensin I. This is in turn cleaved by converting enzyme in the lung, kidney and other tissues to an octapeptide, angiotensin II. Angiotensin II raises blood pressure both directly by causing arteriolar constriction and indirectly by stimulating release of the sodium-retaining hormone aldosterone from the adrenal gland causing a rise in extracellular fluid volume. Inhibitors of renins have been sought as an agent for control of hypertension, congestive heart failure, and hyperaldosteronism.

The present invention concerns novel peptides which inhibit renin. It also concerns pharmaceutical compositions containing these novel peptides, methods of treating renin-associated hypertension, congestive heart failure, and hyperaldosteronism, as well as the use of the peptides as diagnostic tools, and the methods for preparing the peptides.

United States 4,479,941 covers certain renin-inhibitory peptides of the formula

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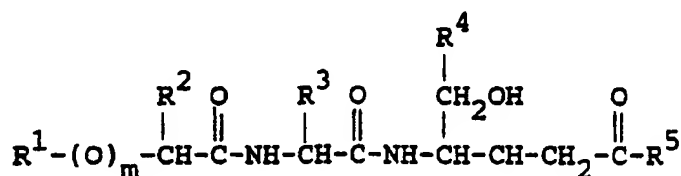
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European Application No. 85/308759 covers certain renin-inhibitory dipeptides of the formula

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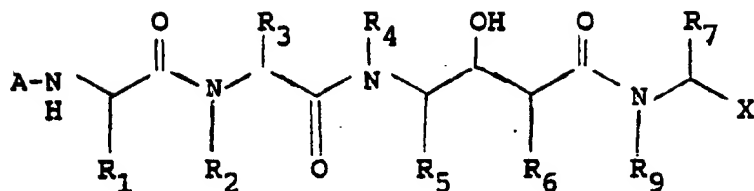


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wherein m is 0 or 1 and R¹-R⁵ are a variety of organic groups.

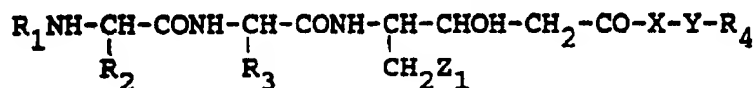
European Application No. 184,855 covers renin-inhibitory peptides of the formula

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wherein A is an N-protecting group; R₁, R₃, R₅ and R₇ are lower alkyl or lipophilic or aromatic amino acid side chains and may be the same or different; R₂, R₄ and R₆ are hydrogen or lower alkyl and may be the same or different; X is hydrogen, lower alkyl or -CH₂-OR₈, wherein R₈ is hydrogen, lower alkyl or alkaryl; and R₉ is lower alkyl, hydroxy, hydroxyalkyl, alkoxy, allyl, alkaryl, or thioalkyl and pharmaceutically acceptable salts thereof.

European Application No. 192,544 covers peptide pepstatin analogues of the formula



wherein R₁ is COR or SO₂R¹; R₂ is optionally substituted lower alkyl, phenyl, naphthyl, cyclohexyl or pyridyl; R₃ is hydrogen, lower alkenyl, phenyl, naphthyl, 3-6C cycloalkyl, monocyclic heterocyclic or substituted lower alkyl; Z₁ is i-Pr, phenyl, cyclohexyl; X-Y is a dipeptide.

European Application No. 220-665 covers peptidyl; amino cycloalkyl; hydroxy alkanolic acid derivatives of the formula



wherein

X = H, R₁OC_mH_{2m}CO, R₁C_mH_{2m}OCO, R₁C_mH_{2m}CO, R₁SO₂, Q-C_rH_{2r}CO, H(NHCH₂CH₂)_mNHCH₂CO or 9-fluorenyl-C_mH_{2m}OCO;

Z = 1-4 peptide-linked amino acid gps. selected from Abu, Ada, Ala, Arg, Asn, Bia, Cal, Dab, Gln, Gly, His, N(im)-alkyl-His, Ile, Leu, tert-Leu, Lys, Met, α-Nal, β-Nal, Nbg, Nie, Orn, Phe, Pro, Ser, Thr, Tic, Trp, Tyr and Val; and

E = OH, OA, NH₂, NHA or N(A)₂.

The compounds are useful as renin and acid protease inhibitors.

SUMMARY OF THE INVENTION

The present invention relates to novel peptides of the formula



and the pharmaceutically acceptable acid addition salts thereof wherein A, X, Y, W, and U are as defined herein below.

The invention also includes pharmaceutical compositions comprising an effective amount of the above peptide of formula I in admixture with a pharmaceutically acceptable carrier or excipient and a method for treating renin-associated hypertension in a patient suffering therefrom comprising administering to said patient the above pharmaceutical composition in unit dosage form.

Further the invention includes a pharmaceutical composition comprising an effective amount of a peptide of formula I above in admixture with a pharmaceutically acceptable carrier or excipient, and a method for treating hyperaldosteronism in a patient suffering therefrom comprising administering to said patient the above pharmaceutical composition in unit dosage form.

Further the invention includes a pharmaceutical composition comprising an effective amount of a peptide of formula I in admixture with a pharmaceutically acceptable carrier or excipient, and a method for treating congestive heart failure in a patient suffering therefrom comprising administering to said patient the

above pharmaceutical composition in unit dosage form.

The present invention also includes the use of peptides of formula I above as diagnostic tools for the identification of cases of hypertension due to renin excess.

The invention further includes methods for preparing peptides of formula I above and novel intermediates used in their preparation.

DETAILED DESCRIPTION

The following table provides a dictionary of the terms used in the description of the invention.

TABLE I

<u>Abbreviated Designation</u>	<u>Amino Acid</u>
LEU	L-Leucine
HIS	L-Histidine
TZA	2(<u>S</u>)-Amino-3-(4-thiazolyl)- propanoic acid (4-Thiazolylalanine)
STA	4(<u>S</u>)-Amino-3(<u>S</u>)-hydroxy-6- methylheptanoic acid








TABLE I (Continued)

5	<u>Abbreviated Designation</u>	<u>Amino Acid</u>
10	PHSTA	4(<u>S</u>)-Amino-3(<u>S</u>)-hydroxy-5-phenylpentanoic acid
15	CYSTA	4(<u>S</u>)-Amino-3(<u>S</u>)-hydroxy-5-cyclohexanepentanoic acid
ILE	PHE	L-Isoleucine
PHE(OBn)	HOMOPHE	L-Phenylalanine
20		L-Phenylalanine benzyl ester
		2(<u>S</u>)-Amino-5-phenylpentanoic acid (Homophenylalanine)
	LYS	L-Lysine
25	MET	L-Methionine
	NAPHTHYLALA	2(<u>S</u>)-Amino-3-(1-naphthyl)-propanoic acid (1-Naphthylalanine)
30	CYCLOHEXYLALA	Cyclohexylalanine (Hexahydro-L-phenylalanine)
	TYR	L-Tyrosine
35	TYR(OMe)	O-Methyl-L-tyrosine
	TRP	L-Tryptophane
	GLN	L-Glutamine
40	(NMe) PHE	N-Methyl-L-phenylalanine
	ASTA	3(<u>RS</u>), 4(<u>S</u>)-Diamino-6-methylheptanoic acid
	ACYS	3(<u>RS</u>), 4(<u>S</u>)-Diamino-5-cyclohexanepentanoic acid
45	CHSTA	4(<u>S</u>)-Amino-3(<u>S</u>)-hydroxy-4-cyclohexanebutanoic acid
50	DFKSTA	4(<u>S</u>)-Amino-3-oxo-2,2-difluoro-6-methylheptanoic acid
	DFSTA	4(<u>S</u>)-Amino-3(<u>S</u>)-hydroxy-2,2-difluoro-6-methylheptanoic acid
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TABLE I (Continued)

10	Abbreviated Designation	Amino Acid (Continued)
15	DFKCYS	4(<u>S</u>)-Amino-3-oxo-2,2-difluoro- 5-cyclohexanepentanoic acid
20	DFCYS	4(<u>S</u>)-Amino-3(<u>S</u>)-hydroxy- 2,2-difluoro-5- cyclohexanepentanoic acid
25	DFKCHS	4(<u>S</u>)-Amino-3-oxo-2,2-difluoro- 4-cyclohexanebutanoic acid
30	DFCHS	4(<u>S</u>)-Amino-3(<u>S</u>)-hydroxy- 2,2-difluoro-4- cyclohexanebutanoic acid
35	ALG	2(<u>S</u>)-Amino-4-pentenoic acid (Allylglycine)
40	PGY	2(<u>S</u>)-Aminopentanoic acid (Propylglycine)
45	PPG	2(<u>S</u>)-Amino-4-pentynoic acid (Propargylglycine)
50	CPM	2(<u>S</u>)-Amino-3- cyclopropanepropanoic acid (Cyclopropylalanine)
55	EMG	2(<u>S</u>)-Amino-4,5(<u>RS</u>)-epoxy-4- pentenoic acid
	BYG	2(<u>S</u>)-Aminohexanoic acid (Butylglycine)
	NIA	2(<u>S</u>)-Amino-3-cyanopropanoic acid (cyanoalanine)

TABLE 1 (Contineud)

5		<u>Amides With</u>
	$-\text{NHCH}_2\text{Ph}$	Benzylamine
10	$-\text{NHCH}_2$ 	Cyclohexylmethylanine
15	$-\text{NHCH}_2$  $-\text{CH}_2\text{NHZ}$ (BOC)	m-Xylene-di-amine (Z or BOC)
20	$-\text{NHCH}_2$  $-\text{CH}_2\text{NH}_2$	m-Xylene-di-amine
25	$-\text{NH}_2$	Ammonia
30	$-\text{NH}$  $\text{N}-\text{CH}_2\text{Ph}$	4-Amino-N-benzylpiperidine
35	$-\text{NH}$  NH	4-Aminopiperidine
40	$-\text{NH}-\text{CH}_2$ 	2-Aminomethylpyridine
	$-\text{NHCH}_2\text{CH}_2-\text{N}$ 	N-(2-Aminoethyl)morpholine
45	$-\text{NHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	2-Methylbutylamine
	$-\text{NHCH}(\text{CH}_2\text{OH})\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	1-Hydroxymethyl- 2-methylbutylamine

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TABLE 1 (Contineud)

5			<u>Protecting Group</u>
	Z	Benzyloxycarbonyl	
	BOC	Tert-butyloxycarbonyl	
10	TR	Triphenylmethyl	
15			<u>Esters With</u>
	-OCH ₃	Methanol	
	-OC ₂ H ₅	Ethanol	
20	-OCH(CH ₃) ₂	2-Propanol	
	-OC(CH ₃) ₃	<u>tert</u> -Butanol	
25			<u>Solvents and Reagents</u>
30	DMF	N,N-Dimethylformamide	
	DMSO	Dimethylsulfoxide	
	HOBT	Hydroxybenzotriazole	
	DCC	N,N'-Dicyclohexylcarbodiimide	
35	HOAc	Acetic acid	
	Et ₃ N	Triethylamine	
	THF	Tetrahydrofuran	
40	CH ₂ Cl ₂	Dichloromethane	

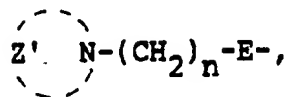
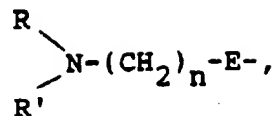
The peptides of the present invention are represented by the formula



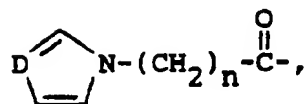
and the pharmaceutically acceptable acid addition salts thereof, wherein A is

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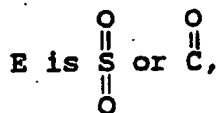
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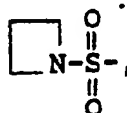
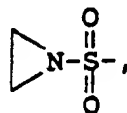
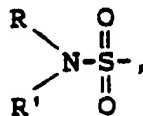


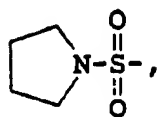
wherein R and R' are each independently hydrogen or lower alkyl;



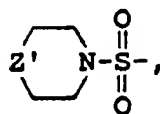
is a saturated ring of from 1 to 5 carbon atoms
 wherein Z' is CH₂, O, S, or NR,
 n is an integer of from 0 to 3; and
 D is N, S, O, or CH.

Examples of A may be but are not limited to the following:

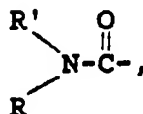




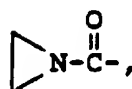
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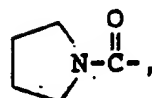
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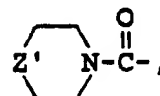
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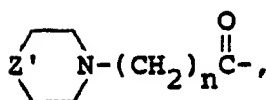
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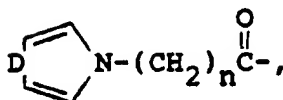
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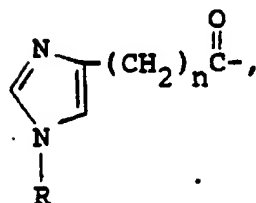
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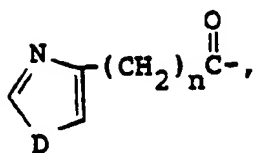
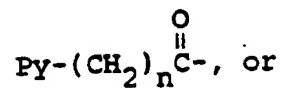


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wherein R and R' are each independently hydrogen or lower alkyl,

Z' is CH₂, O, S, NH, NR with R defined as above;

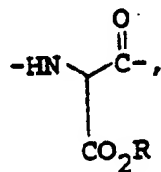
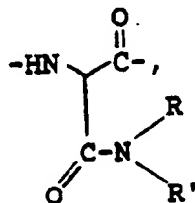
n is 0-3;

D is N, S, O, CH;

Py is 2-pyridyl, 3-pyridyl, or 4-pyridyl.

X is PHE, HOMOPHE, TYR, TYR(OMe), NAPHTHYLALA, CYCLOHEXYLALA, LEU, TRP, HIS, or (NMe)PHE;

Y is GLN, HIS, LEU, PGY, MET, TZA, ALG, PPG, CPM, EMG, BYG, NIA,



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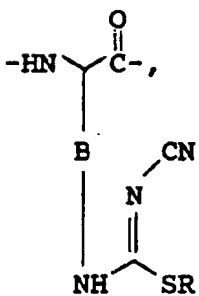
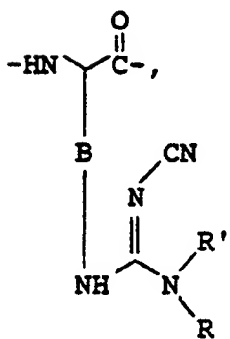
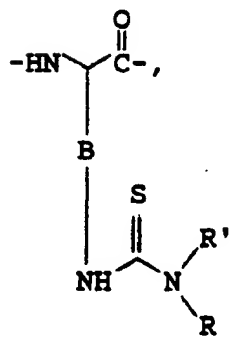
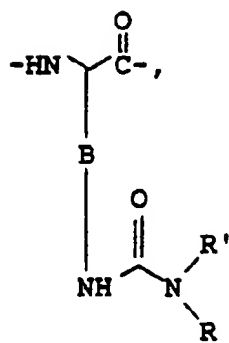
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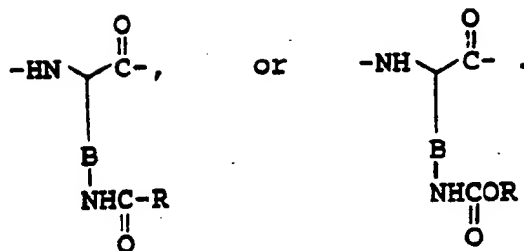
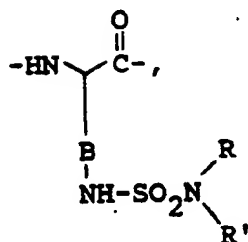
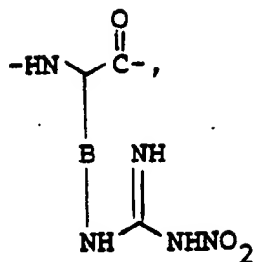
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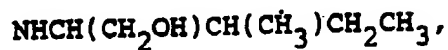
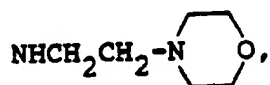
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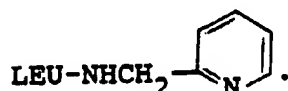
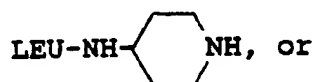
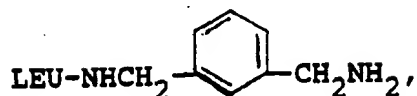
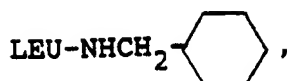




wherein R and R' are each independently H, benzyl, or lower alkyl; B is a chain of from three to six carbon atoms which is saturated, olefinic, or acetylenic;

W is STA, CYSTA, or PHSTA, CHSTA, DFKSTA, DFKCYS, DFKCHS, ASTA, ACYS;
U is





Preferred compounds of the present invention are those

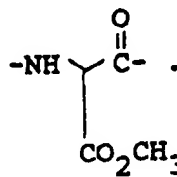
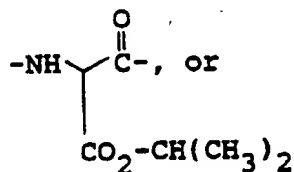
wherein A is $\text{Me}_2\text{N-E-}$, $\langle\text{cyclopentyl}\rangle\text{-N-E}$, $\langle\text{piperidine}\rangle\text{-N-E}$, or $\langle\text{piperidine}\rangle\text{-N-CH}_2\text{-CO-}$;

X is PHE TYR(OMe) or NAPHTHYLALA, W is STA, CHSTA, DFKCYS,

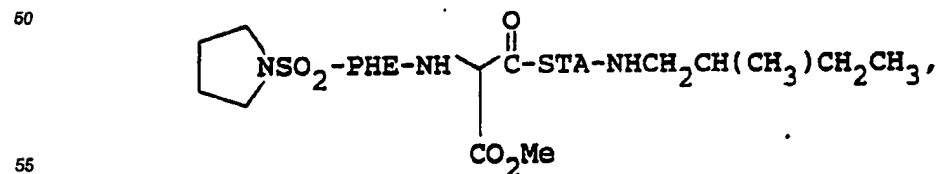
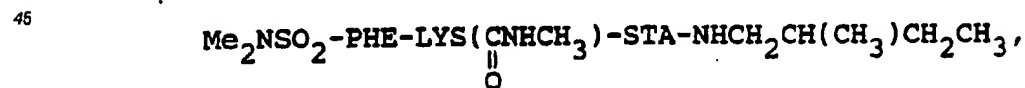
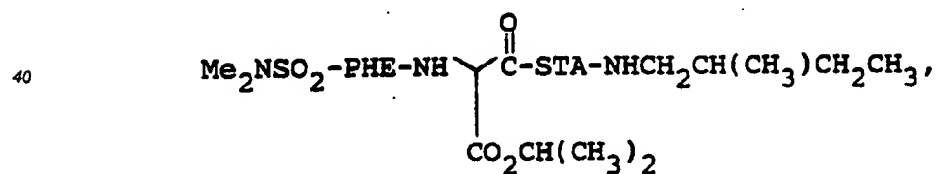
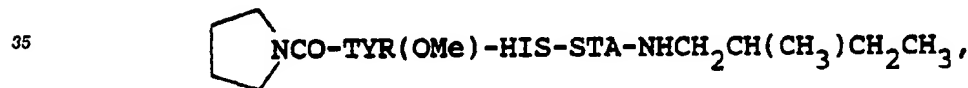
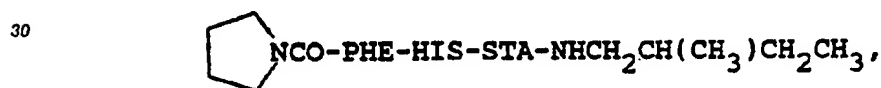
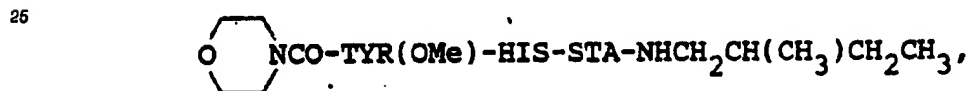
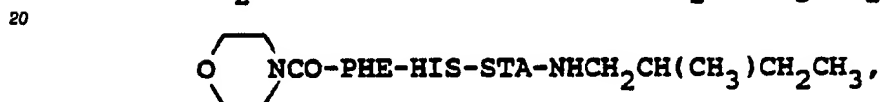
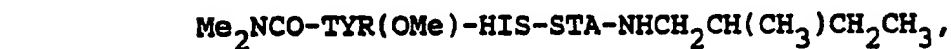
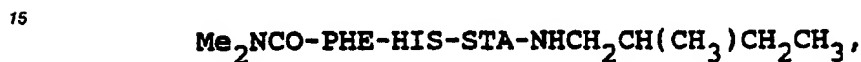
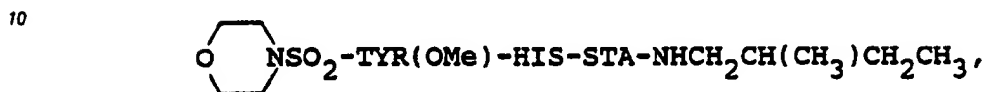
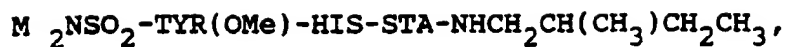
DFKSTA or CYSTA, U is $\text{NHCH}_2\text{CH}_2\text{-}\langle\text{piperidine}\rangle\text{-O}$ or $\text{NHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$,

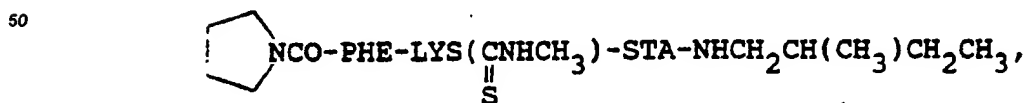
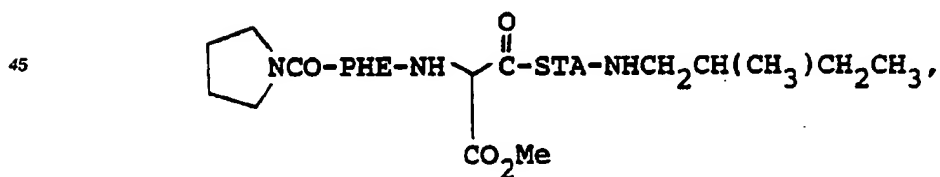
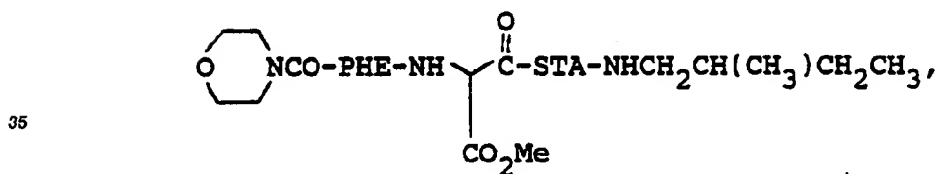
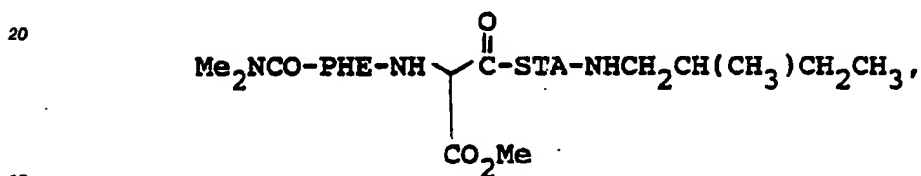
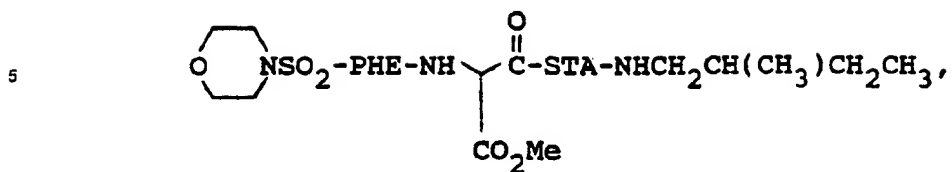
and Y is HIS, $\text{LYS}(\text{CNHCH}_3)$, $\text{LYS}(\text{CNHCH}_3)$, $\text{LYS}(\text{CNHCH}_3)$,

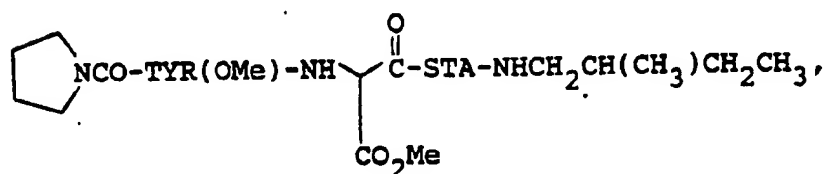
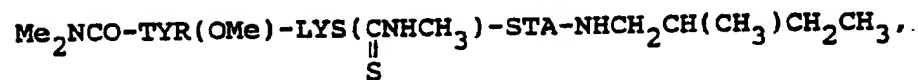
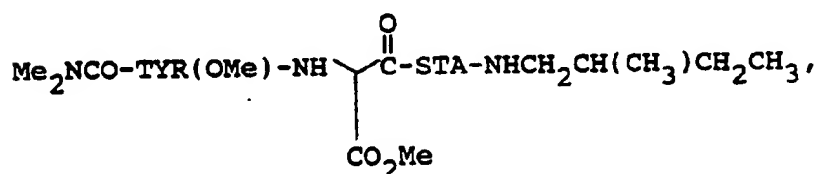
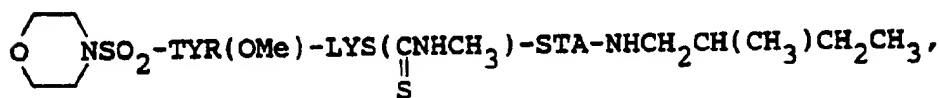
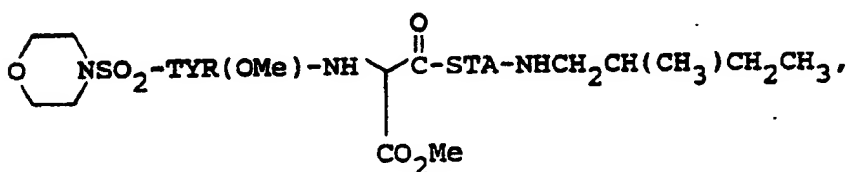
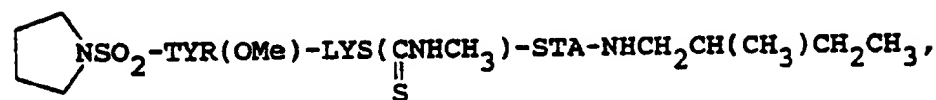
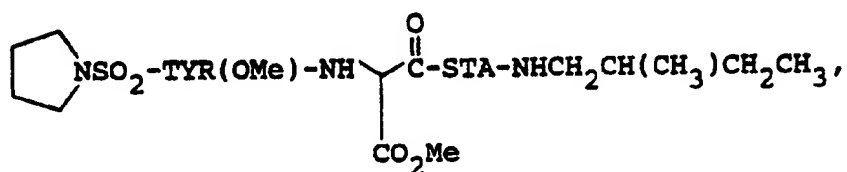
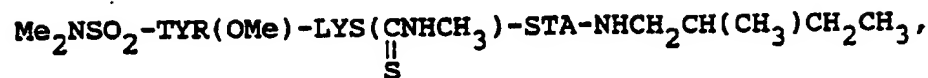
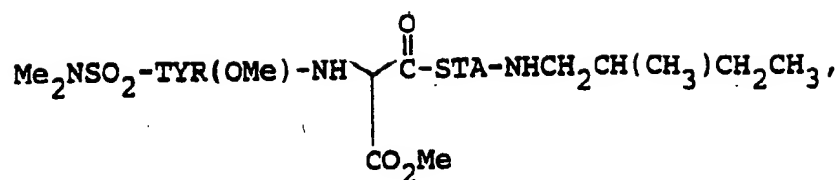
$\text{LYS}(\text{CNHNO}_2)$, TZA, ALG, PGY,

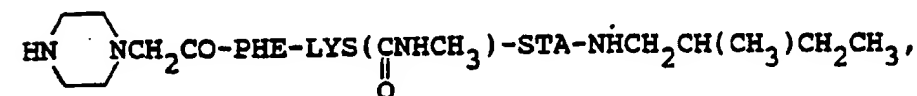
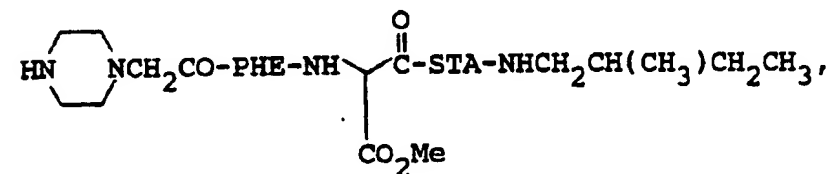
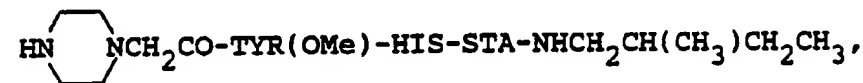
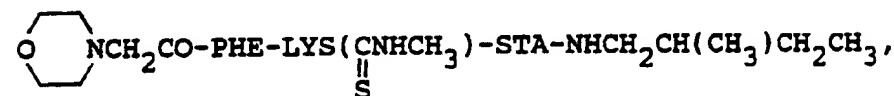
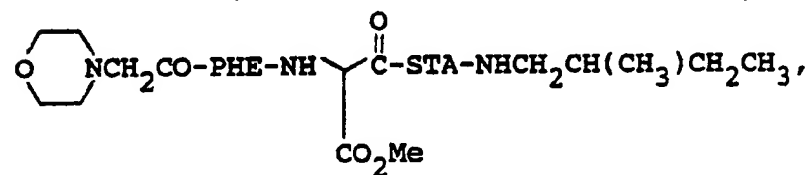
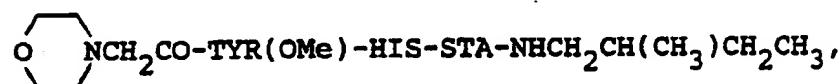
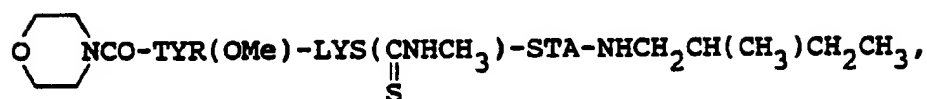
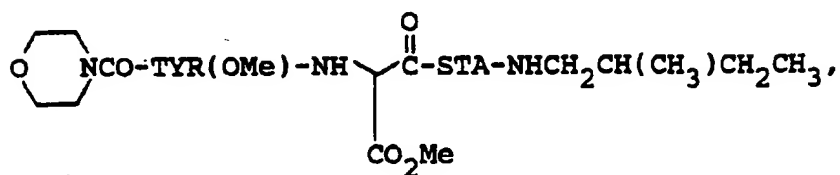
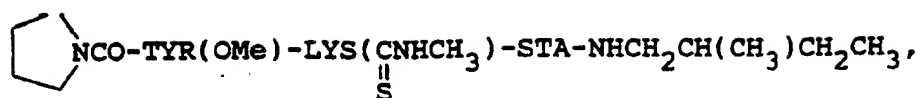


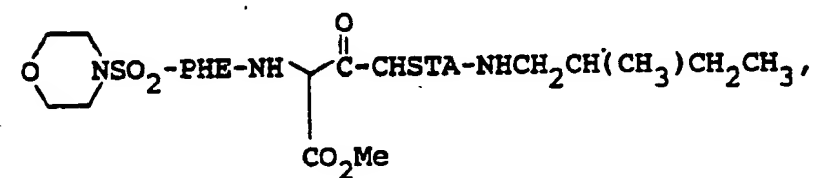
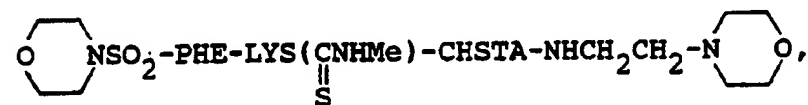
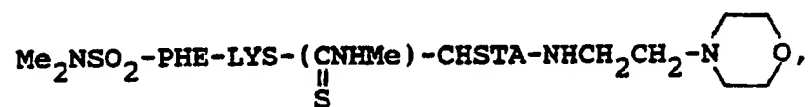
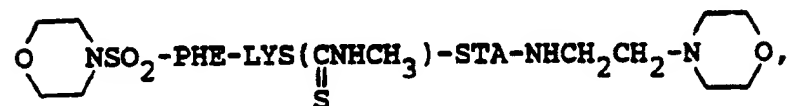
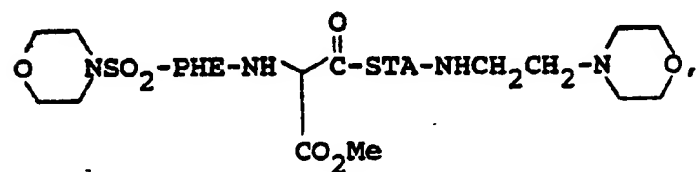
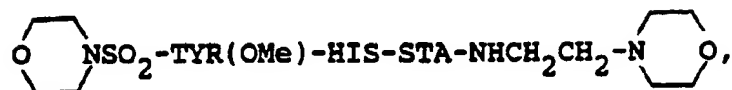
Particularly valuable compounds falling within the scope of the invention include the following:

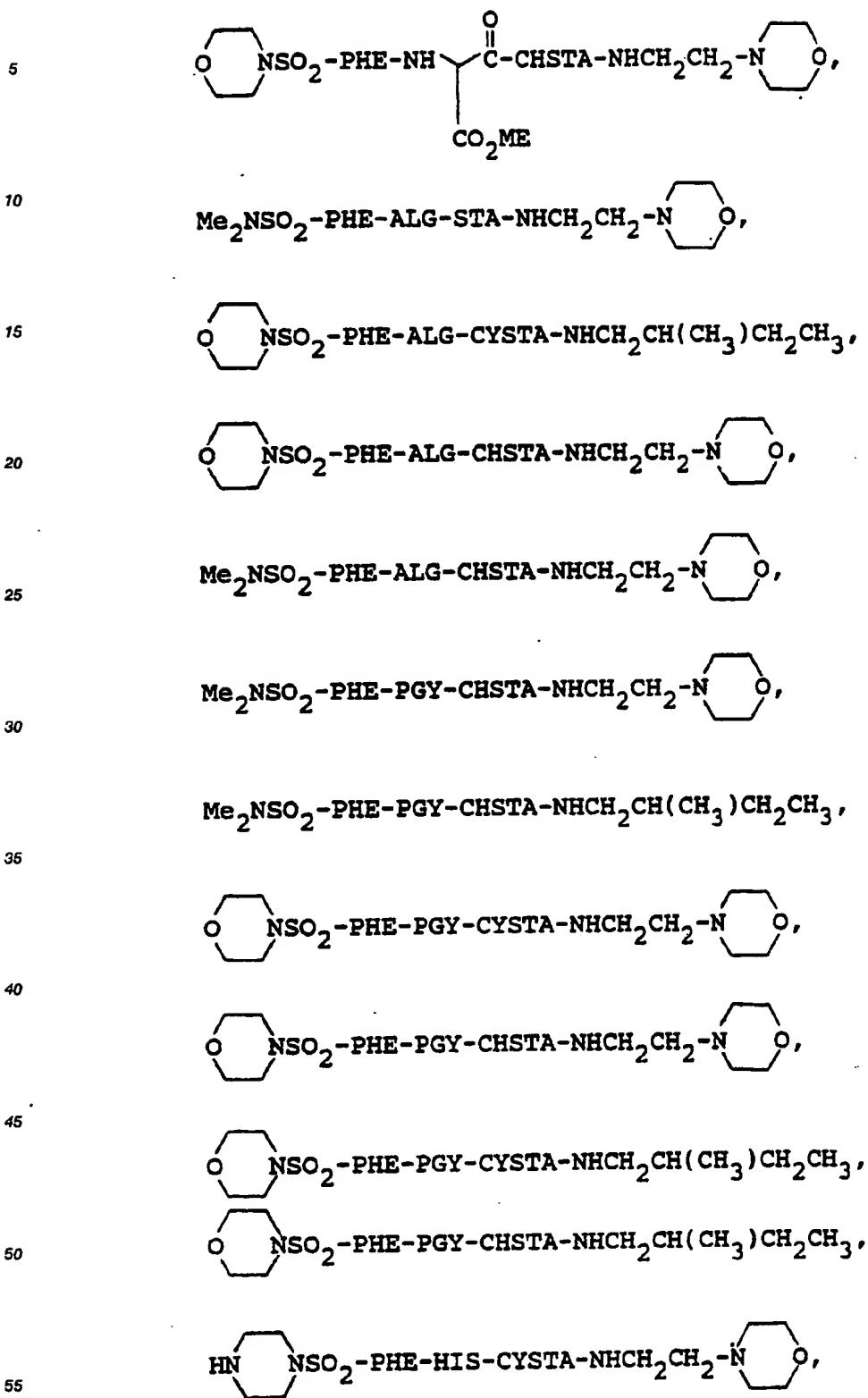


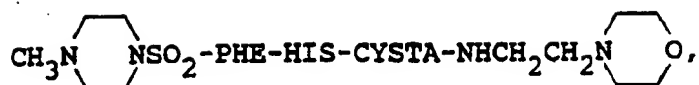












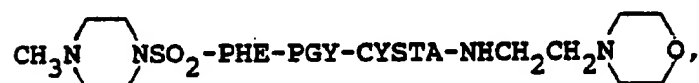
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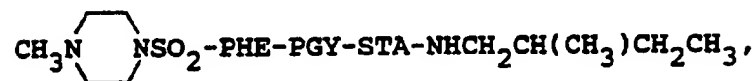
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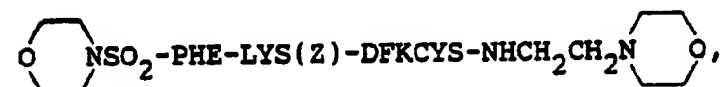
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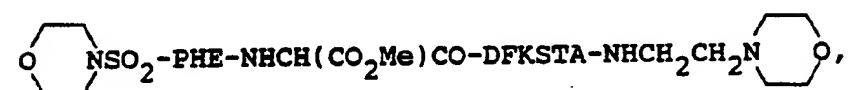
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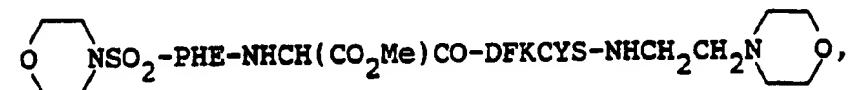
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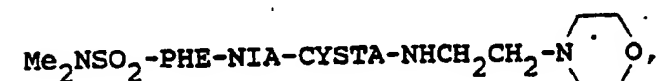
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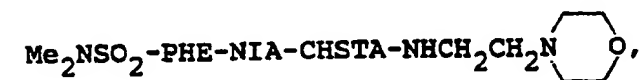
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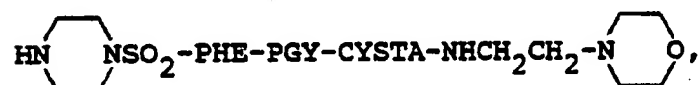
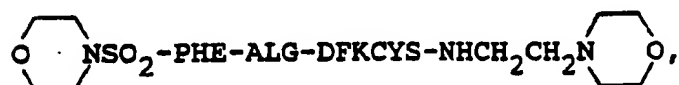
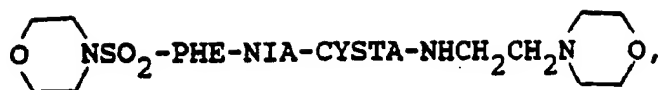


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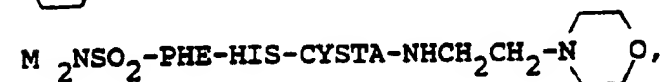
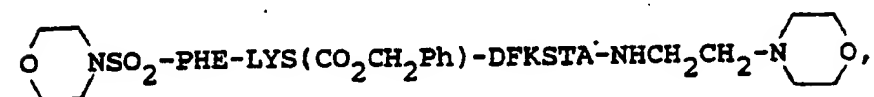
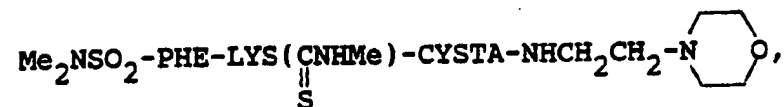
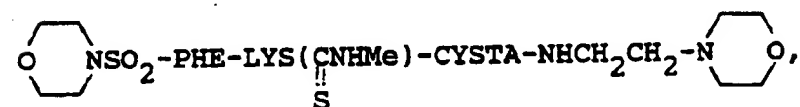
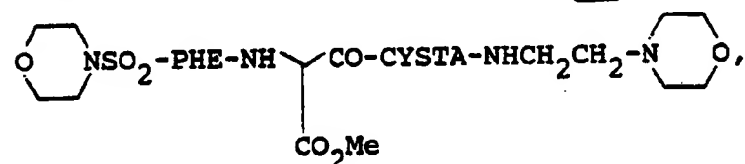
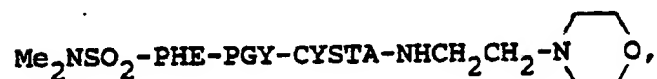
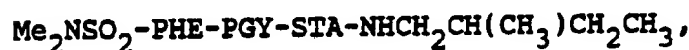
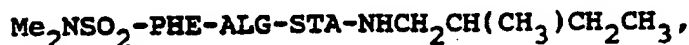
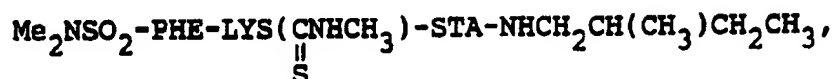
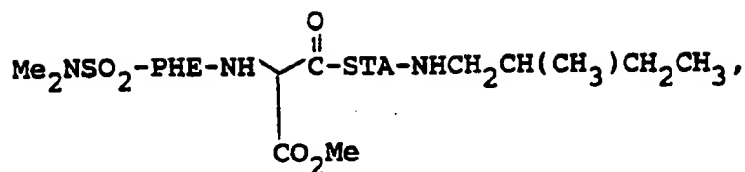
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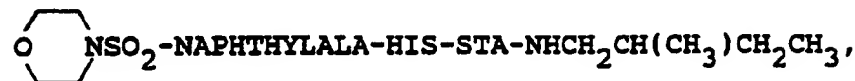
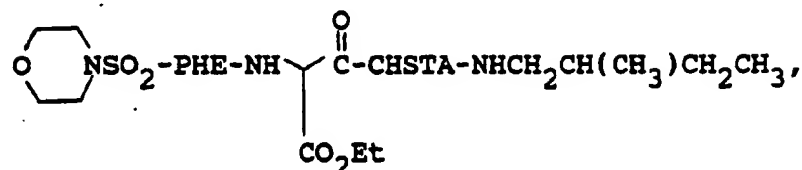




Most preferred compounds of the invention are:







The compounds of the present invention have the advantage of increased hydrophilicity relative to renin inhibitors known in the art. This property makes the compound more readily absorbed.

The compounds include solvates and hydrates and pharmaceutically acceptable acid addition salts of the basic compounds of formula I above.

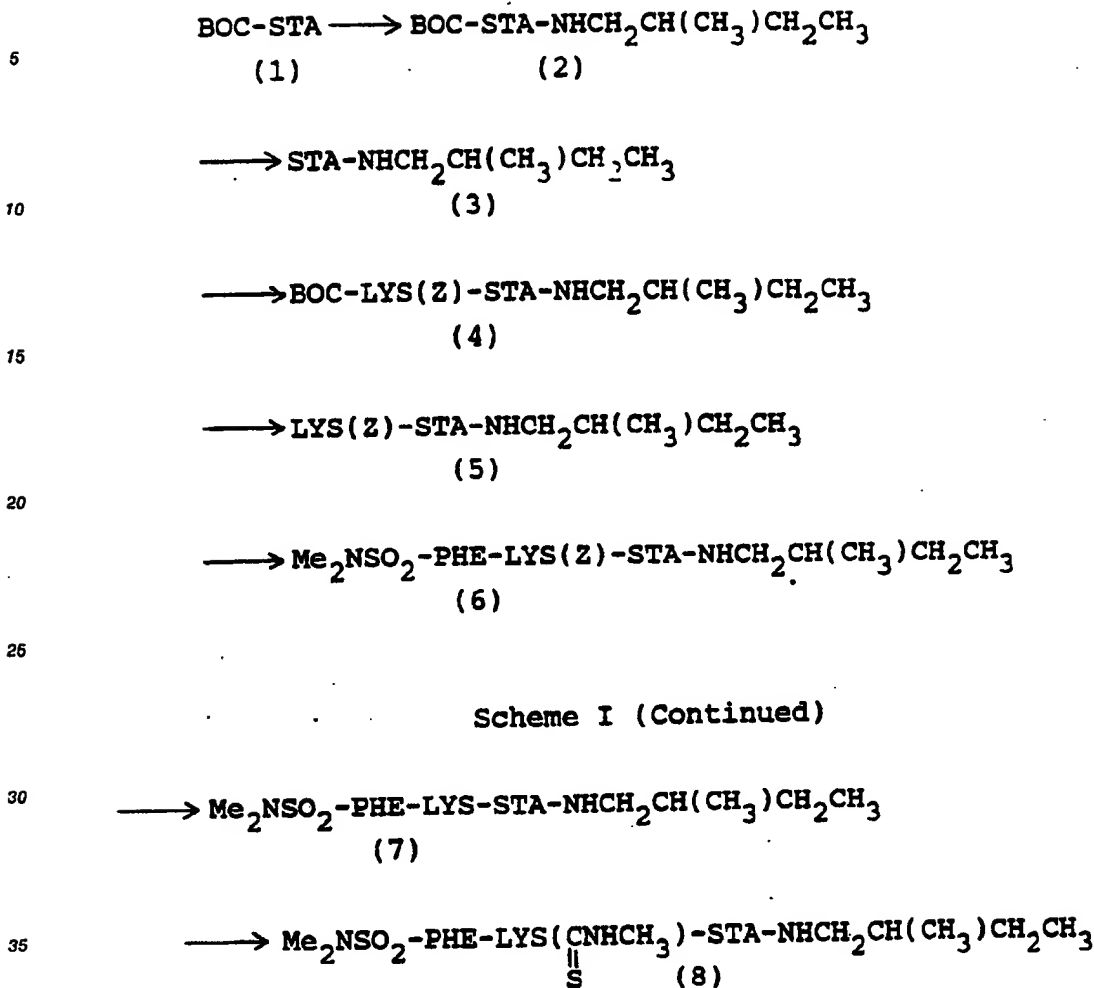
The term pharmaceutically acceptable acid addition salt is intended to mean a relatively nontoxic acid addition salt either from inorganic or organic acids such as, for example, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, benzoic, gluconic, fumaric, succinic, ascorbic, maleic, tartaric, methanesulfonic, and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt form with a base. Unless otherwise specified the L form is the preferred embodiment.

The modified peptides of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

Some of the above novel peptides may be prepared in accordance with well-known procedures for preparing peptides from their constituent amino acids. Other of the novel peptides of the present invention are prepared by a step-wise procedure or by a fragment coupling procedure depending upon the particular final product desired.

The following scheme illustrates novel methods of preparing certain peptides of the present invention.

Scheme I



According to Scheme I above, BOC-protected statine (1) is reacted with DCC, HOBT, and a primary amine, for example, 2-methylbutylamine, to form the corresponding BOC-protected compound (2). The reaction takes place in an inert solvent such as methylene chloride, tetrahydrofuran, chloroform, dioxane, or ethyl acetate. The preferred solvent is methylene chloride. The reaction time varies from 1 to 24 hours. Preferably it takes about 2 to 6 hours. The reaction temperature may also vary from about 15°C to 30°C. Preferably it is approximately 25°C.

The above compound (2) is reacted with a strong acid such as trifluoroacetic, HBr, or HCl to remove the BOC-protecting group thus forming corresponding compound (3) with a free amino terminus. Preferably HCl is used.

Compound 3 is then reacted with BOC-protected LYS(Z) to form the corresponding compound (4). This reaction takes place in an inert solvent, for example DMF, with DCC, HOBT, and triethylamine as activating agents at temperatures of from 0°C to 25°C. The reaction may take as long as 72 hours.

This compound (4) is reacted with a strong acid, such as trifluoroacetic acid, to form the corresponding compound with a free amino terminus (5). The reaction takes place in an inert solvent, preferably dichloromethane, at about 25°C, taking from 0.5 to 2 hours.

This compound (5) is reacted with L-N,N-dimethylsulfamylphenylalanine, DCC, and HOBT in an inert solvent such as DMF at approximately room temperature for from 4 to 24 hours to form the Z-protected tripeptide (6). The Z group is then removed by catalytic hydrogenation in a polar, inert solvent such as methanol forming peptide (7). The catalyst is preferably palladium on carbon.

This peptide (7) is reacted with an acylating agent such as methyl isocyanate, methyl isothiocyanate,

acetyl chloride, methyl chloroformate, N,N-dimethylsulfamyl chloride, or 2-methyl-1-nitro-2-thiopseudourea at about room temperature in an inert solvent such as methylene chloride to form a compound of the present invention (8).

For compounds of the types illustrated in Examples 3-15 other amino acid derivatives such as a protected HIS derivative (e.g. N α -trityl N α -(Z)), a BOC-protected allylglycine or a BOC-protected aminomalonate monomethyl ester are substituted for the protected LYS derivative in the conversion of statine derivative (3) to dipeptide (4). Additionally, carbamyl or acyl amino acid derivatives may be substituted for sulfamyl amino acid derivatives in the conversion of dipeptide (5) to tripeptide (6). Finally, amides of CYSTA, CHSTA, DFSTA, DFCYS or DFCYS may replace STA amides.

Sulfamyl amino acid derivatives are prepared by reaction of a sulfamyl chloride with the desired amino acid in a mixture of aqueous base and organic solvents at 0 to 40°C. Bases include NaOH, NaHCO₃, Na₂CO₃, KOH, KHCO₃, K₂CO₃. Organic solvents include THF, dioxane, and acetonitrile.

Alternatively, sulfamyl amino acids are prepared by reaction of a sulfamyl chloride with the tetraalkylammonium salt of the desired amino acid in anhydrous organic solvents at 0 to 40°C. Salts include tetra-n-butylammonium, tetra-n-propylammonium, tetra-ethylammonium, tetra-methylammonium and benzyl-trimethylammonium. Organic solvents include THF, dioxane, 1,2-dimethoxyethane, acetonitrile, 2-propanol, t-butanol, chloroform, dichloromethane and 1,2-dichloroethane.

Carbamyl amino acid derivatives are prepared by reaction of a carbamyl chloride, organic base, and an amino acid ester in an aprotic solvent, followed by saponification or hydrogenolysis of the ester. Bases include triethyl amine, diisopropyl ethyl amine, pyridine, and 4-dimethylaminopyridine. Solvents include dichloromethane, THF, chloroform, acetonitrile, and dioxane.

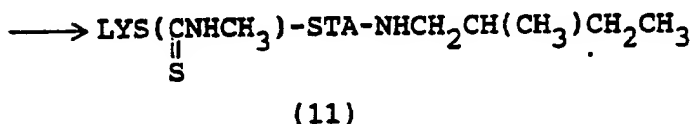
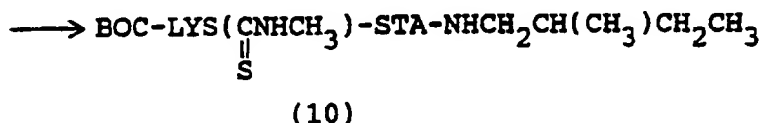
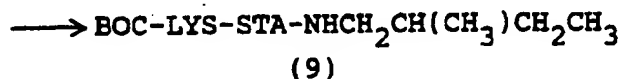
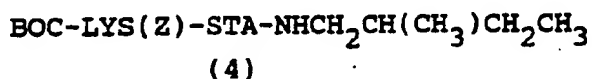
An alternative method of synthesis is shown in Scheme II wherein BOC-LYS(Z)-STA-NHCH₂CH(CH₃)-CH₂CH₃ (4), prepared as in Scheme I, is treated with hydrogen and palladium on carbon catalyst in an inert, polar solvent such as methanol to give the compound with a free amino side chain (9).

Acylation of this compound (9) with acylating agents such as in the final step of the previous method affords LYS-derivatized peptides such as the thiourea (10).

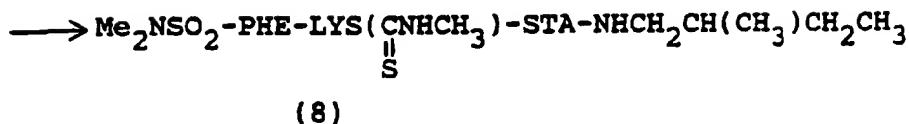
This compound (10) is treated with strong acid such as methanolic hydrogen chloride in an inert solvent, preferably dichloromethane, at about 25°C, taking 10 to 60 minutes to remove the BOC-protecting group.

The resulting compound (11) is reacted with an amino acid derivative such as L-N,N-dimethylsulfamyl-phenylalanine, DCC, and HOBT in a polar solvent such as DMF, at about 25°C, for 24 to 48 hours to form a compound of the present invention (8).

Scheme II



Scheme II (Continued)



10 The strategy of peptides chain assembly and selection and removal of protecting groups is discussed in Chapter 1, "The Peptide Bond," in "The Peptides. Analysis, Synthesis, Biology," E. Gross and J. Meienhofer, Eds., Academic Press, New York, NY, 1979, pp. 42-44.

The DCC/HOBT method of coupling is well-known to those skilled in the art and is discussed in Chapter 5, "The Carbodiimide Method" by D.H. Rich and J. Singh in "The Peptides. Analysis, Synthesis, Biology,"
15 E. Gross and J. Meienhofer, Eds., Academic Press, New York, NY, 1979, pp. 42-44.

Peptide coupling depends on activating the carboxy terminus and condensing it with another peptide containing a free amino terminus. In addition to the DCC coupling method described above, other methods of activating the carboxyl group of a protected amino acid include:

- 1) The azide method - described in Chapter 4 of the above reference.
- 20 2) The mixed anhydride method - described in Chapter 6 of the above reference.
- 3) The active ester method - described in Chapter 3 of the above reference.

The invention includes a process for the preparation of compounds of formula I wherein A is



30 which comprises reacting at least two equivalents of a sulfamyl chloride with at least one equivalent of amino acid as in X, an inorganic aqueous base and a water-miscible organic solvent to give a sulfamyl-amino acid, followed by coupling of the latter to the -Y-W-U fragment and converting if desired to a pharmaceutically acceptable acid addition salt thereof by known means.

35 The invention also includes a second process for the preparation of compounds of formula I where A is



40 which comprises reacting at least two equivalents of a tetra-alkylammonium salt of an amino acid with one equivalent of a sulfamyl chloride in anhydrous organic solvents to give a sulfamyl amino acid, followed by
45 coupling of the latter to the -Y-W-U fragment and converting, if desired, to a pharmaceutically acceptable addition salt thereof by known means.

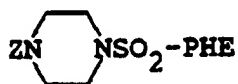
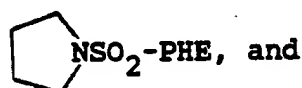
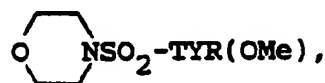
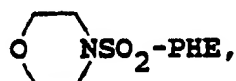
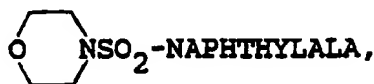
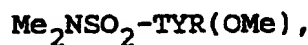
The invention also includes a process for the preparation of compounds of formula I wherein A is



50 which comprises reacting at least one equivalent of a carbamyl chloride with at least one equivalent of an amino acid benzyl ester as in X, an organic base and an aprotic organic solvent to produce a carbamyl amino acid benzyl ester, hydrogenolysis in the presence of a noble metal catalyst to give a carbamyl amino acid, and subsequent coupling of the latter to the -Y-W-U fragment and converting if desired to a

pharmaceutically acceptable acid addition salt thereof by known means.

The invention also includes novel sulfamyl-amino acid intermediates including specifically:



as both the free acid and as salts prepared from alkaline earth metals, ammonia and organic amines, especially dicyclohexylamine.

35 The compounds of the present invention are useful for treating renin-associated hypertension, congestive heart failure, and hyperaldosteronism. They are also useful as diagnostic tools for determining the presence of renin-associated hypertension or hyperaldosteronism.

40 The term lower alkyl refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms including but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, 2-methylhexyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl, and the like.

45 Pharmaceutical compositions which comprise an effective amount of the compound in combination with a pharmaceutically acceptable carrier are part of the present invention. An important aspect of the present invention is a method of treating renin-associated hypertension in a mammal which comprises administering a pharmaceutical composition containing an effective amount of a compound of the invention in combination with a pharmaceutically acceptable carrier to the mammal.

Another equally important aspect of the present invention is a method of treating hyperaldosteronism in a mammal which comprises administering a pharmaceutical composition containing an effective amount of a compound of the invention in combination with a pharmaceutically acceptable carrier to the mammal.

50 An additional aspect of the present invention is a method for treating congestive heart failure in a mammal which comprises administering a pharmaceutical composition containing an effective amount of a compound in combination with a pharmaceutically acceptable carrier to the mammal.

55 The effectiveness of the aforementioned compounds is determined by a test for in vitro renin inhibitory activity. This activity is determined by a standard radioimmunoassay for angiotensin I. In this assay the enzyme, renin, incubated for two hours at 37° in the presence of a substrate, angiotensinogen, generates the product, angiotensin I. Test compounds are added to the incubation mixture. Relative activity is reported as the IC₅₀, which is the molar concentration of test compound causing a 50% inhibition of the renin activity.

Table II



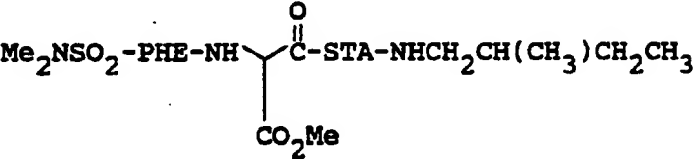
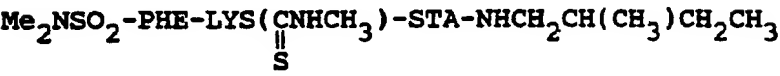



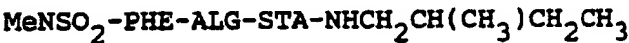


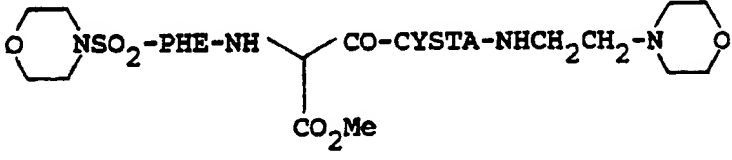
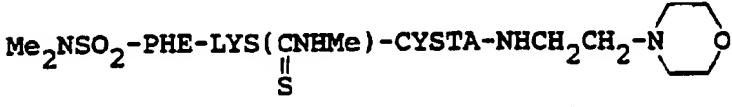
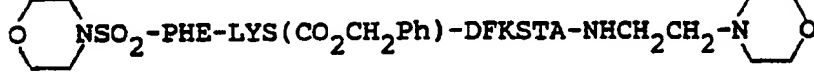
5	<u>Compound</u>	<u>IC₅₀ (M)</u>
	$\text{Me}_2\text{NSO}_2\text{-PHE-HIS-STA-NHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	4.1×10^{-8}
10	 $\text{NSO}_2\text{-PHE-HIS-STA-NHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	2.0×10^{-8}
15	$\text{Me}_2\text{NSO}_2\text{-TYR(OMe)-HIS-STA-NHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	$\approx 3.0 \times 10^{-6}$
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Table II (Continued)

5	<u>Compound</u>	<u>IC₅₀ (M)</u>
10		5.8×10^{-8}
15		2.5×10^{-8}
20		2.5×10^{-8}
25		3.3×10^{-7}
30		4.9×10^{-7}
35		2.5×10^{-7}
40		7.0×10^{-9}
40		1.5×10^{-9}
40		1.1×10^{-9}
45		4.0×10^{-9}
50		2.0×10^{-8}
55		2.2×10^{-9}

5

Table II (Continued)














<u>Compound</u>	<u>IC₅₀ (M)</u>
10 Me ₂ NSO ₂ -PHE-HIS-CYSTA-NHCH ₂ CH ₂ -N 	2.0X10 ⁻⁸
15  NSO ₂ -PHE-HIS-CHSTA-NHCH ₂ CH(CH ₃)CH ₂ CH ₃	4.8X10 ⁻⁹
20  NSO ₂ -PHE-NH  CO-CHSTA-NHCH ₂ CH(CH ₃)CH ₂ CH ₃ CO ₂ Et	3.2X10 ⁻⁸
25  NSO ₂ -PHE-HIS-CYSTA-NHCH ₂ CH ₂ -N 	5.0X10 ⁻⁹
30  NSO ₂ -NAPHTHYLALA-HIS-STA-NHCH ₂ CH(CH ₃)CH ₂ CH ₃	3.0X10 ⁻⁹
35 HN  NSO ₂ -PHE-HIS-STA-NHCH ₂ CH(CH ₃)CH ₂ CH ₃	3.5X10 ⁻⁷
40 CH ₃ N  NSO ₂ -PHE-HIS-STA-NHCH ₂ CH(CH ₃)CH ₂ CH ₃	1.5X10 ⁻⁷
45  NSO ₂ -PHE-NIA-STA-NHCH ₂ CH(CH ₃)CH ₂ CH ₃	2.5X10 ⁻⁸
Me ₂ NSO ₂ -PHE-PGY-STA-NHCH ₂ CH ₂ -N 	3.2X10 ⁻⁷
Me ₂ NSO ₂ -PHE-PGY-STA-NHCH ₂ CH(CH ₃)CH ₂ CH ₃	3.4X10 ⁻⁸
60 Me ₂ NSO ₂ -PHE-HIS-STA-NHCH ₂ CH ₂ -N 	≈9X10 ⁻⁷
55 Me ₂ NSO ₂ -PHE-ALG-STA-NHCH ₂ CH ₂ -N 	1.6X10 ⁻⁷

Table II (Continued)

Compound	IC_{50} (M)
$ \begin{array}{c} \text{O} \quad \text{NSO}_2\text{-PHE-NH} \quad \text{CO-STA-NHCH}_2\text{CH}_2\text{-N} \quad \text{O} \\ \\ \text{CO}_2\text{Me} \end{array} $	1.3×10^{-7}
$ \text{O} \quad \text{NSO}_2\text{-PHE-HIS-STA-NHCH}_2\text{CH}_2\text{-N} \quad \text{O} $	3.0×10^{-7}
$ \text{Z-N} \quad \text{NCO-PHE-HIS-STA-NHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3 $	1.4×10^{-7}

As can be seen from the above table, the compounds of the present invention have a significant effect on the activity of renin and thus are useful for the treatment of hypertension, hyperaldosteronism, and congestive heart failure.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powder and tablets preferably contain from 5 to 10 to about 70 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, tragacanth, methylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

The compound of the present invention may be administered orally, buccally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby solidify.

Liquid form preparations include solutions, suspensions, and emulsions. As an example may be mentioned water or water/propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethyleneglycol solution. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions, and emulsions. These particular solid form preparations are most conveniently provided in unit dosage form and as such are used to provide a single liquid dosage unit. Alternately, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon, or other

volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. The liquid utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol, and the like, as well as mixtures thereof. Naturally, the liquid utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

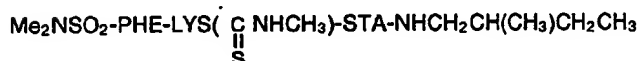
Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 500 mg, preferably 5 to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as renin inhibitors, the mammalian dosage range for a 70 kg subject is from 1 to 1500 mg/kg of body weight per day or preferably 25 to 750 mg/kg of body weight per day optionally in divided portions. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with small dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

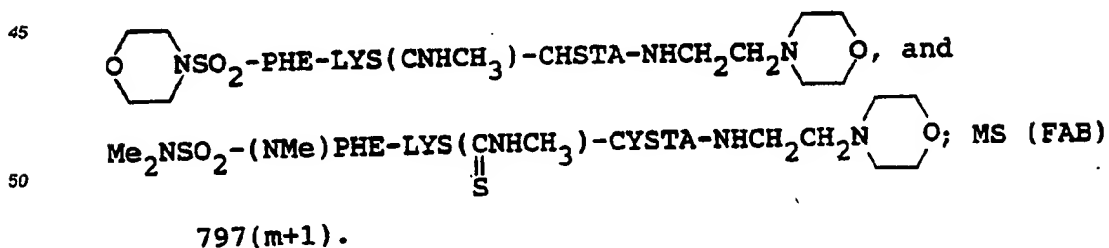
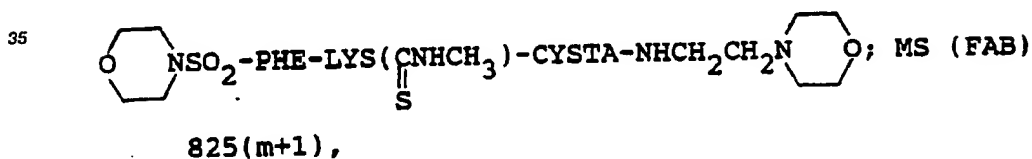
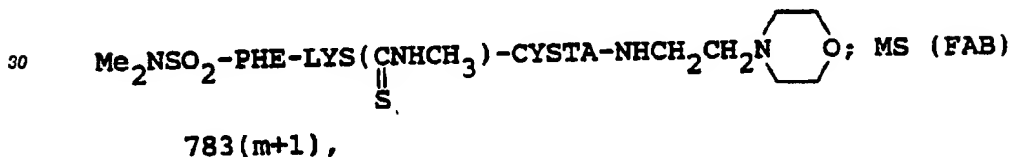
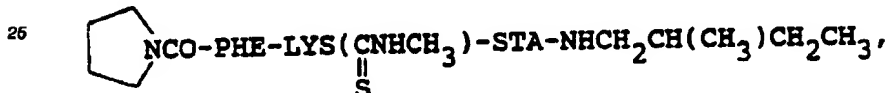
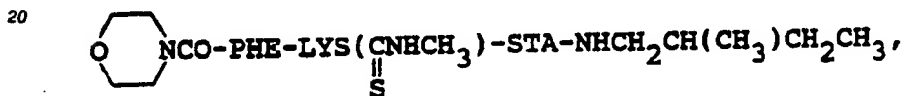
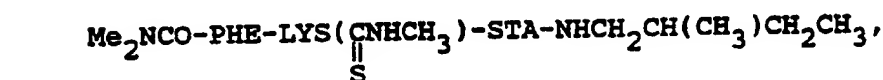
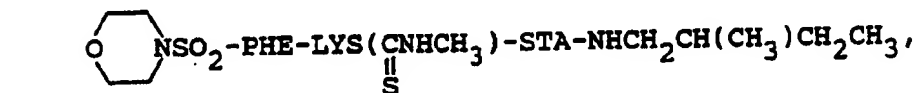
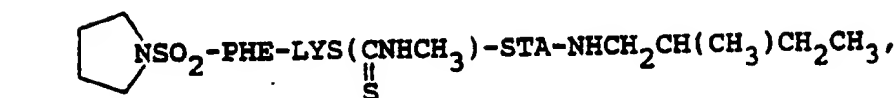
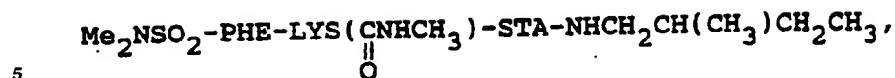
The following examples are provided to enable one skilled in the art to practice the present invention. These examples are not intended in any way to limit the scope of the invention but are illustrative thereof.

EXAMPLE 1



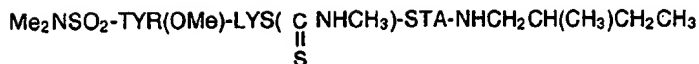
A mixture of $\text{Me}_2\text{NSO}_2\text{-PHE}$ (0.55 g), DCC (0.42 g), $\text{HOBT} \cdot \text{H}_2\text{O}$ (0.27 g), and DMF (10 ml) was stirred at 25° for ten minutes. The resulting suspension was treated with a solution of $\text{LYS}(\text{CSNHCH}_3)\text{-STA-NHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ (0.89 g) in DMF (10 ml). The reaction mixture was stirred for twenty-four hours at 25° and filtered. The filtrate was concentrated under a vacuum and the residue was dissolved in CH_2Cl_2 (60 ml). This solution was washed with 5% aqueous Na_2CO_3 , dried over MgSO_4 , and evaporated. The major product was isolated by flash chromatography on silica gel, eluting with $\text{CHCl}_3\text{-MeOH}$ (99:1). Purified product was evaporated from CH_2Cl_2 solution to give a crisp foam. MS (FAB) 700 ($m + 1$). (FAB is fast atom bombardment.)

The following compounds are obtained in an analogous manner:



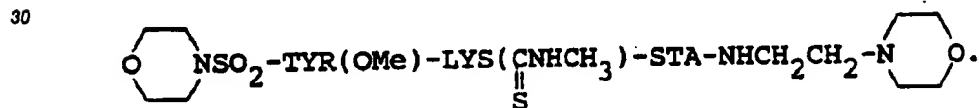
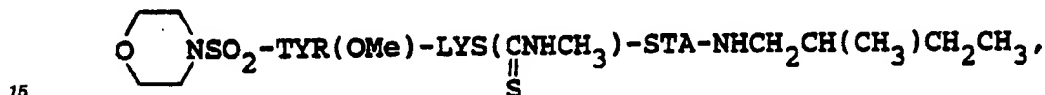
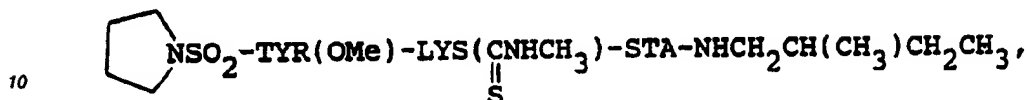
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EXAMPLE 2



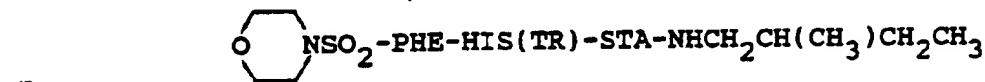
Substitution of $\text{Me}_2\text{NSO}_2\text{-TYR(OMe)}$ for $\text{Me}_2\text{NSO}_2\text{-PHE}$ in Example 1 affords this analogous product.
 5 MS (FAB) 730 ($m+1$).

The following compounds are obtained in an analogous manner:



EXAMPLE 3

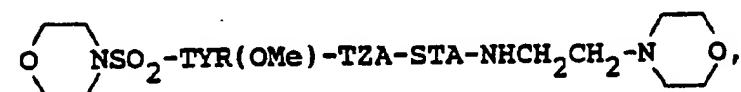
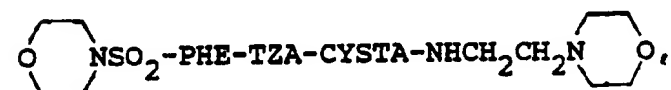
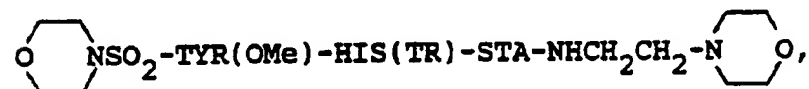
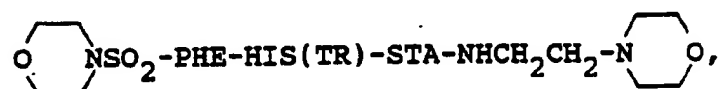
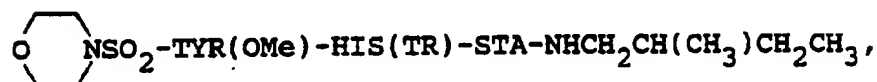
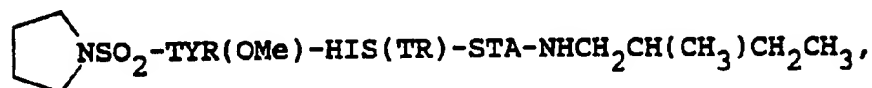
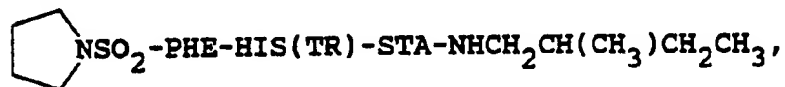
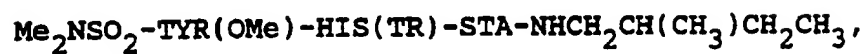
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A mixture of morpholinosulfamyl-PHE (0.63 g), DCC (0.42 g), HOBT·H₂O (0.27 g), and DMF (10 ml) was stirred at 25° for ten minutes. The resulting slurry was treated with a solution of HIS(TR)-STA-NHCH₂CH(CH₃)CH₂CH₃ (1.25 g) in DMF (5 ml). After stirring twenty-four hours at 25° the reaction mixture
 50 was filtered and concentrated under vacuum. The residue was dissolved in CH₂Cl₂ (75 ml) and this solution was washed with 5% aqueous Na₂CO₃ (25 ml), dried over MgSO₄, and evaporated. The major product was isolated by flash chromatography on silica gel, eluting with CHCl₃-MeOH (99:1) to give a crisp foam (1.3 g) upon vaporation from CH₂Cl₂ solution. TLC R_f = 0.57 (silica gel, CHCl₃-MeOH (9:1)).

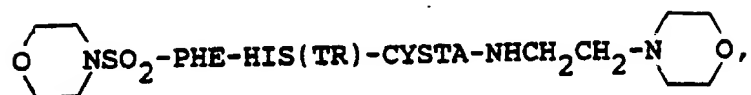
The following compounds are obtained in an analogous manner:

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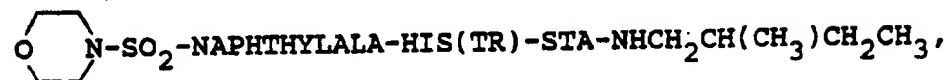




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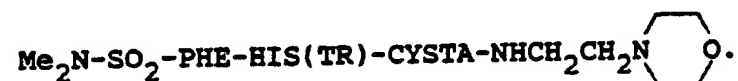
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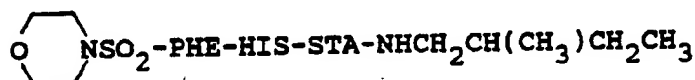
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EXAMPLE 4

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35 A solution of trityl-protected tripeptide from Example 3 above (1.3 g) in 80% acetic acid (10 ml) was heated in a steam bath until the solution temperature remained above 90° for three minutes. The hot solution was diluted with water (15 ml) and the resulting precipitate was removed by filtration. The aqueous filtrate was evaporated at reduced pressure and the residue was partitioned between CH₂Cl₂ (75 ml) and 10% aqueous Na₂CO₃ (30 ml). The organic layer was dried over MgSO₄ and evaporated to a crisp foam (0.87 g). MS (FAB) 678 (m + 1).

40 The following compounds are obtained in an analogous manner:

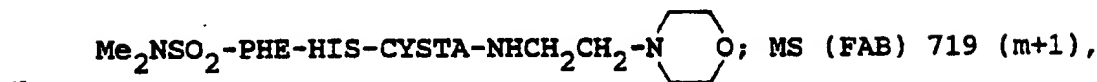
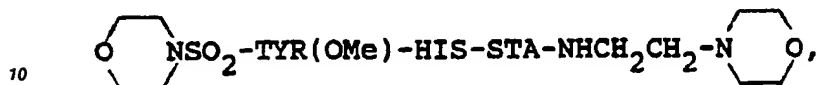
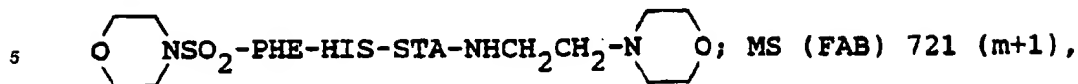


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EXAMPLE 5



Substitution of $\text{Me}_2\text{NSO}_2\text{-PHE}$ in Example 3 give the analogous trityl-protected tripeptide which was deprotected as in Example 4 to afford $\text{Me}_2\text{NSO}_2\text{-PHE-HIS-STA-NHCH}_2\text{CH(CH}_3\text{)CH}_2\text{CH}_3$. MS (FAB) 636 (m+1).

EXAMPLE 6



Substitution of pyrrolidinosulfamyl-PHE in Example 3 gives th analogs trityl-protected tripeptide which was deprotected as in Example 4 to afford pyrrolidinosulfamyl-PHE-HIS-STA-NHCH₂CH(CH₃)CH₂CH₃. MS (FAB) 662 (m+1).

EXAMPLE 7

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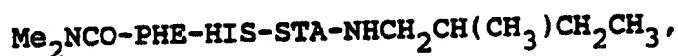


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Substitution of morpholinocarbonyl-PHE in Example 3 gives the analogous trityl-protected tripeptide which was deprotected as in Example 4 to afford morpholinocarbonyl-PHE-HIS-STA-NHCH₂CH(CH₃)-CH₂CH₃. MS (FAB) 642 (m + 1).

The following compounds are obtained in an analogous manner:

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EXAMPLE 8

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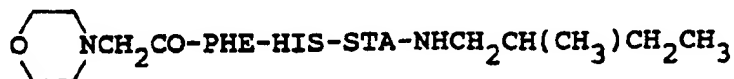
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Substitution of pyrrolidinocarbonyl-PHE in Example 3 gives the analogous trityl-protected tripeptide which was deprotected as in Example 4 to afford pyrrolidinocarbonyl-PHE-HIS-STA-NHCH₂CH(CH₃)-CH₂CH₃. MS (FAB) 626 (m + 1).

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EXAMPLE 9

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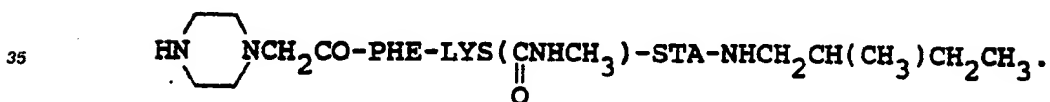
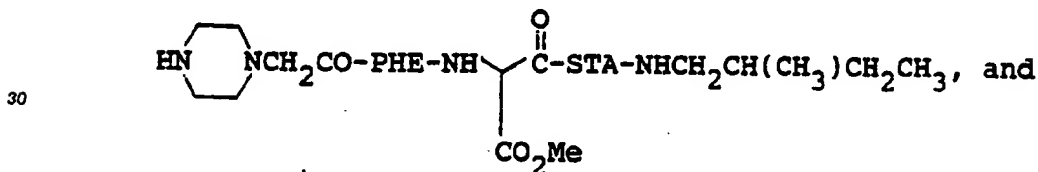
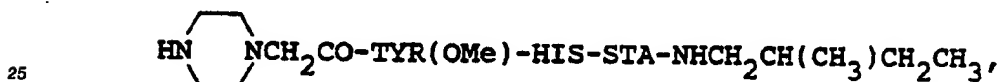
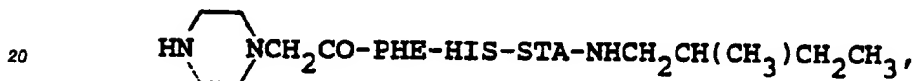
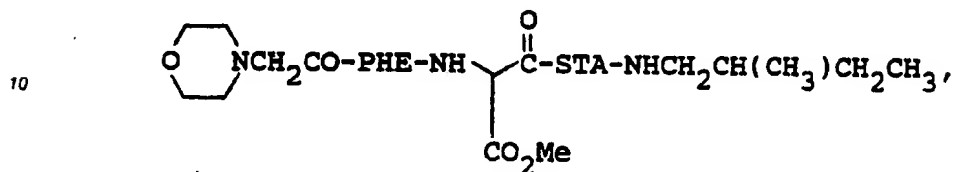
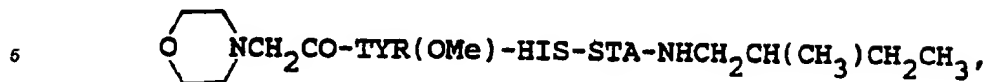


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Substitution of morpholinoacetyl-PHE in Example 3 gives the analogous trityl-protected tripeptide which was deprotected as in Example 4 to afford morpholinoacetyl-PHE-HIS-STA-NHCH₂CH(CH₃)-CH₂CH₃. MS

(FAB) 656 (m + 1).

The following compounds are obtained in an analogous manner:



EXAMPLE 10

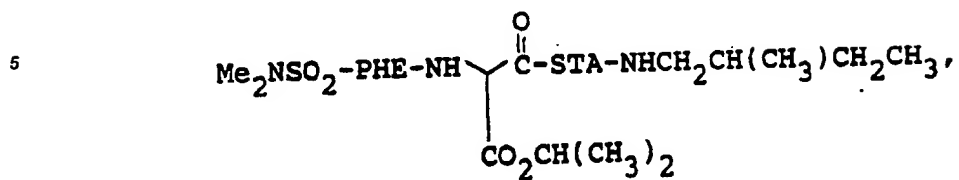


Me₂NSO₂-PHE (1.13 g) and HOBT·H₂O (0.58 g) were dissolved in a mixture of CH₂Cl₂ (100 ml) and DMF (8 ml). After cooling the mixture to 0°, a solution of H₂NCH(CO₂Me)CO-STA-NHCH₂CH(CH₃)CH₂CH₃ (1.49 g) in CH₂Cl₂ (20 ml) was added, followed by addition of DCC (0.88 g). The mixture was stirred at 0° for several hours, then allowed to warm to 23° overnight. The resulting suspension was filtered and the filtrate was evaporated to an oil. This oil was dissolved in ethyl acetate and refiltered. The filtrate was washed consecutively with 1 N citric acid, brine, saturated aqueous NaHCO₃, and brine. The organic phase was then dried over MgSO₄ and evaporated to a waxy solid (2.85 g). Chromatography on silica gel, eluting with CHCl₃-ethyl acetate (1:1) affords the major product as a crisp foam which was suspended in ethyl ether and evaporated, giving a semicrystalline solid (1.95 g).

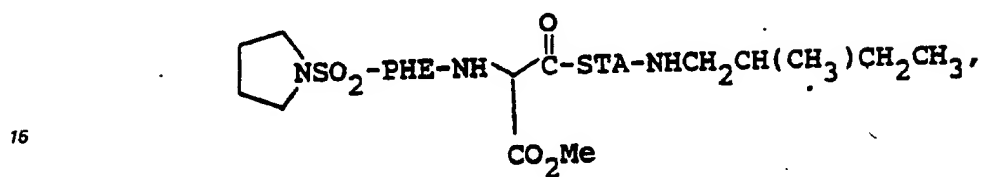
Calcd. for C₂₈H₄₇N₅O₈S·0.03CHCl₃·0.25H₂O:C, 54.14; H, 7.70; N, 11.26; Cl, 0.51; H₂O, 0.72; S, 5.16

Found C, 54.22; H, 7.70; N, 11.27; Cl, 0.52; H₂O, 0.98; S, 5.55.

The following compounds are obtained in an analogous manner:



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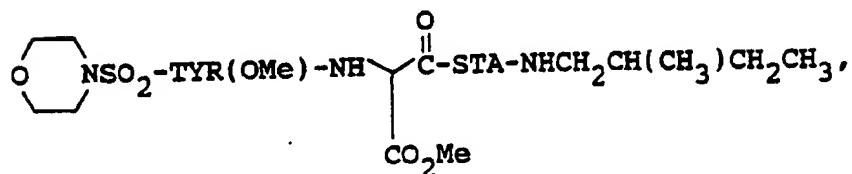
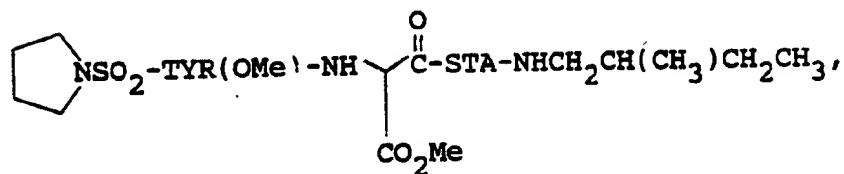
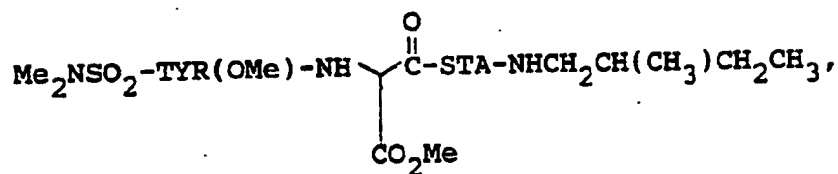
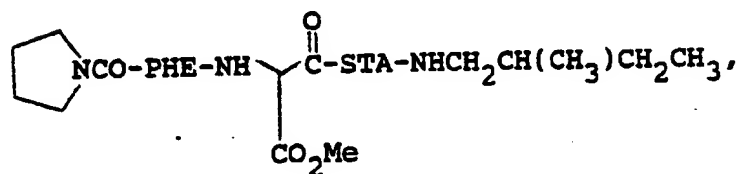
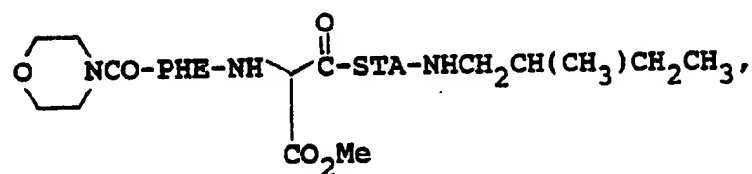
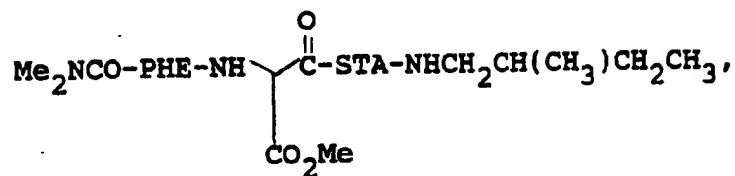
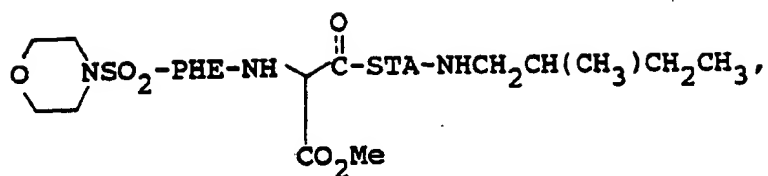
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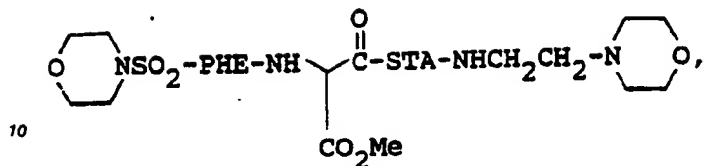
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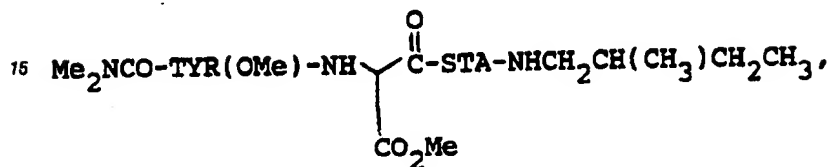
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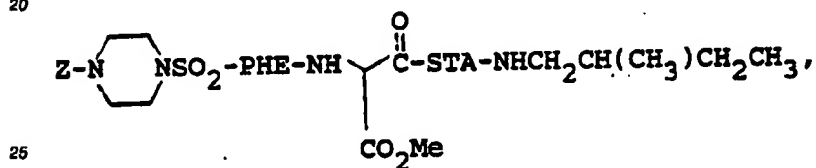
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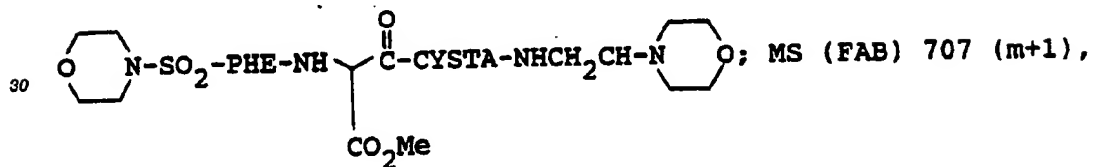
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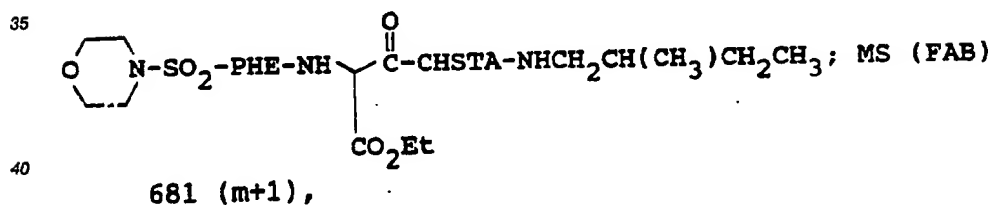
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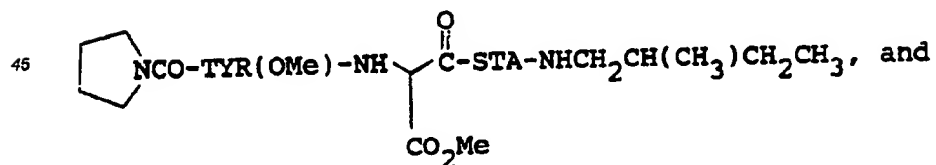
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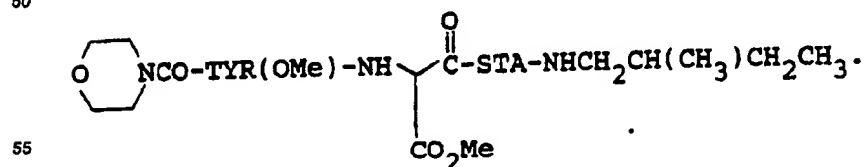
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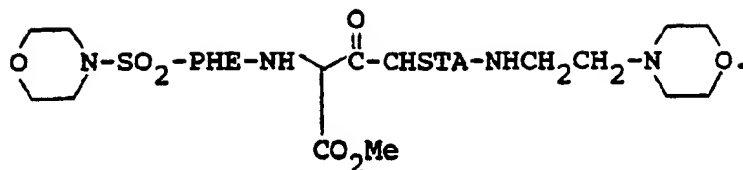


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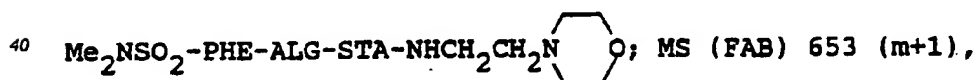
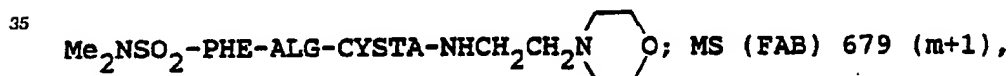
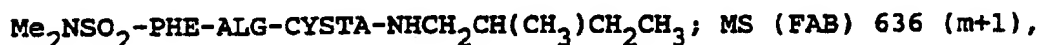


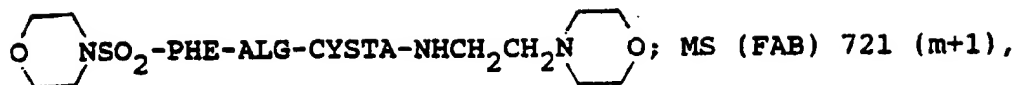
EXAMPLE 11



A solution of BOC-ALG-STA-NHCH₂CH(CH₃)CH₂CH₃ (2.09 g) in a mixture of trifluoroacetic acid (10 mL) and CH₂Cl₂ (20 mL) was stirred for 2 hours at room temperature. The solution was concentrated, taken up in CH₂Cl₂, and re-concentrated. The residue was taken up in CH₂Cl₂ and treated for several minutes with HCl(g). The solution was concentrated to yield an oil which was taken up in 30 ml of DMF and treated with (iPr)₂NEt until basic. The solution was treated with HOBt·H₂O (0.67 g) and cooled in an ice bath. The mixture was treated with Me₂NSO₂-PHE (1.29 g) and DCC (1.04 g), stirring in an ice bath for 2 hours and then overnight at room temperature. After filtering, the filtrate was concentrated under high vacuum. The residue was taken up in EtOAc and washed with 1N citric acid, brine, saturated NaHCO₃, and brine. After drying over Na₂SO₄, the solution was concentrated to yield a tan solid which was purified by flash chromatography (EtOAc) to yield 1.26 g (44.7%) of a foam. MS (FAB) 596 (m+1).

The following compounds are prepared in an analogous manner:

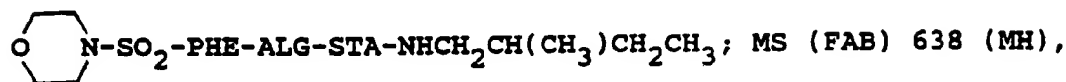




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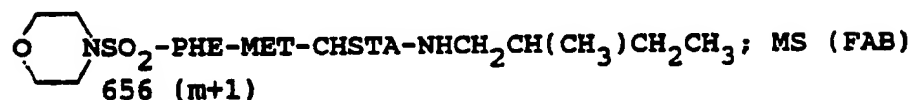
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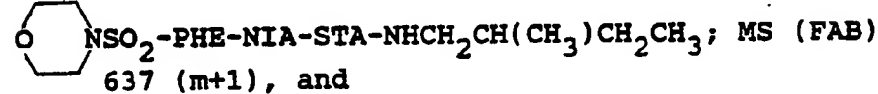
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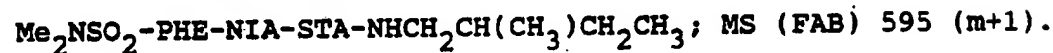
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EXAMPLE 12

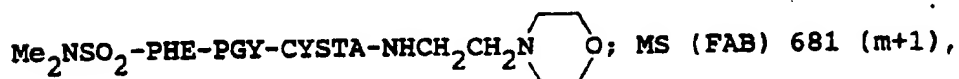
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A solution of the corresponding ALG adduct from Example 11 was reduced by catalytic hydrogenation in methanol, using 5% Pd on carbon catalyst. MS (FAB) 598 (m + 1).

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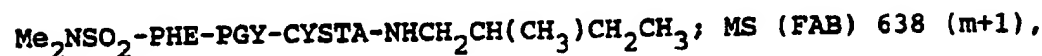
The following compounds are prepared in an analogous manner:

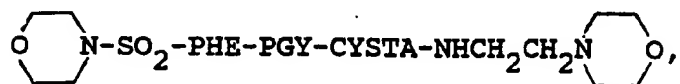
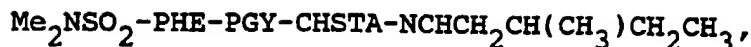


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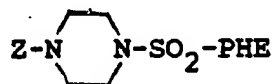
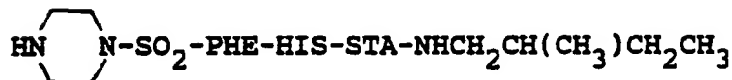


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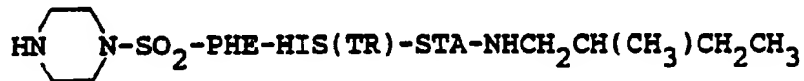




EXAMPLE 13

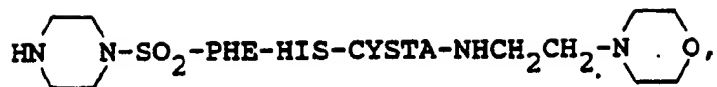


(1.3 g) was coupled to HIS(TR)-STA-NHCH₂CH(CH₃)CH₂CH₃ (1.9 g) according to the method of Example 3. The resulting product (2.5 g) was dissolved in methanol (75 mL), treated with 20% Pd on carbon (0.5 g) and placed under an atmosphere of hydrogen, stirring vigorously for 2 hours. Filtration and evaporation of the filtrate gave



which was treated with 80% acetic acid according to the method of Example 4 to give the desired product. MS (FAB) 677 (m+1).

The following compounds are prepared in an analogous manner.



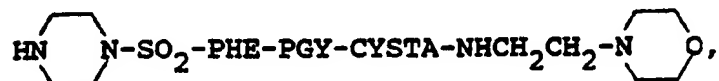
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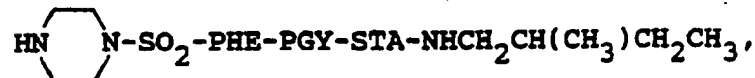
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EXAMPLE 14

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A solution of

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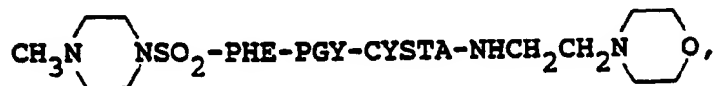
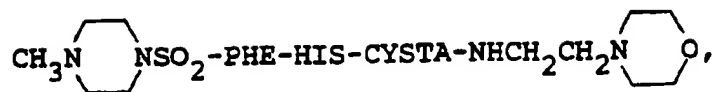


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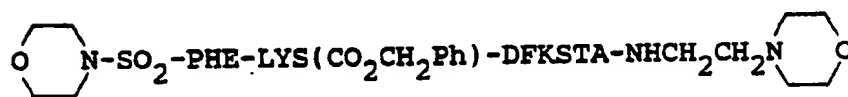
(740 mg) in ethanol (10 mL) was treated with 37% aqueous formaldehyde (0.5 mL) and formic acid (5 mL). The resulting solution was heated at reflux for 3 hours. After cooling the reaction mixture was evaporated and the residue was partitioned between ethyl acetate and 10% K_2CO_3 . The organic layer was dried over MgSO_4 , evaporated and chromatographed to give the N-m thylated product (690 mg). MS (FAB) 691 ($m+1$).

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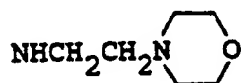
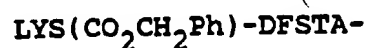
The following compounds are prepared in an analogous manner:



EXAMPLE 15

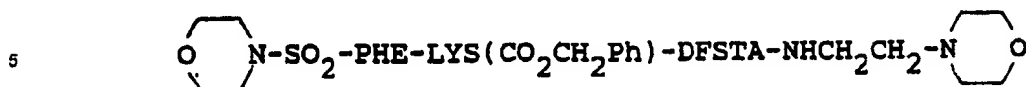


To N-morpholinosulfamyl-L-phenylalanine (0.80 g, 2.55 mmol) and 1-hydroxybenzotriazole hydrate (346 mg, 2.56 mmol) in DMF (30 μ l) at 0° C was added dicyclohexylcarbodiimide (528 mg, 2.56 mmol) in DMF (5 ml) portionwise. After complete addition



(1.50 g, 2.56 mmol) in DMF (15 ml) was added to the solution and the reaction stirred for 1 hour at 0° C before allowing to warm to room temperature. After stirring for about 16 hours, the precipitated dicyclohexylurea was removed by filtration and the DMF evaporated under high vacuum. The resulting residue was taken up in ethyl acetate and washed with 1M aqueous sodium hydroxide solution, followed by brine. After

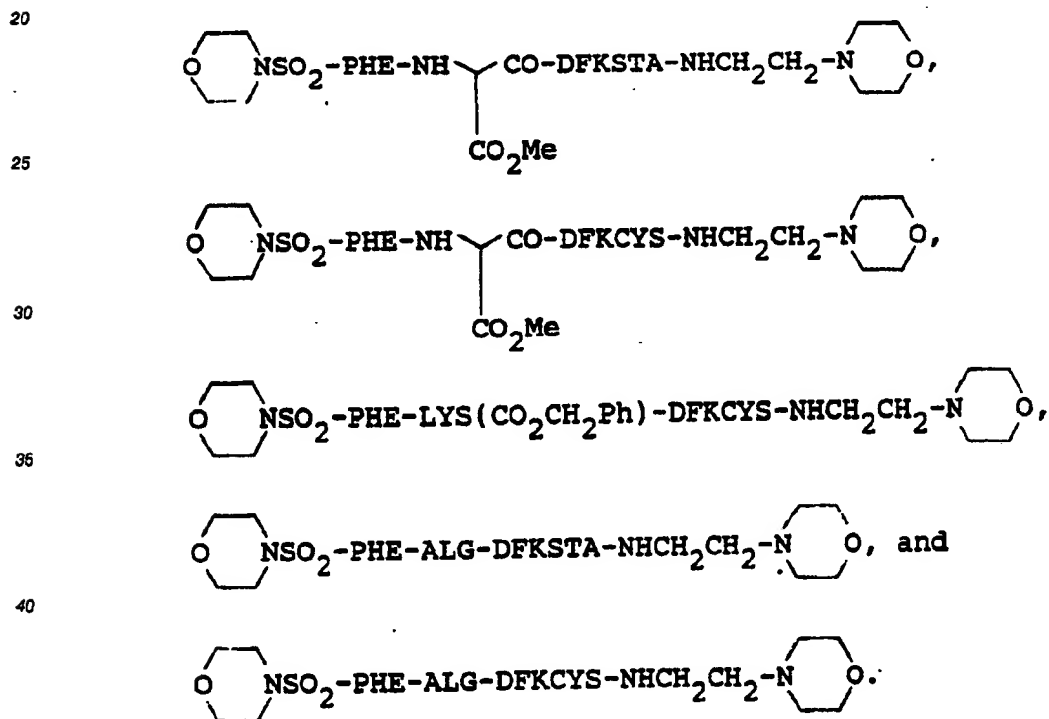
drying (Na_2SO_4), the solvent was removed under reduced pressure. Column chromatography on silica gel employing 5 - 10% methanol/chloroform afforded



(2.00 g, 88.5%) as a white foam. MS (FAB) 882 ($m+1$).

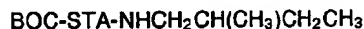
10 To oxalyl chloride (64.4 μl , 0.74 mmol) in dry dichloromethane (5 ml) at -70°C was added dry distilled dimethylsulfoxide (106 μl , 1.50 mmol) and the solution stirred for 10 minutes. The product from the previous reaction (0.50 g, 0.57 mmol) in dichloromethane (5 ml) was then added and the resulting solution stirred at between -60 and -50°C for 30 minutes. The reaction was then allowed to reach -30°C and stirred for 30 minutes before precooling to -70°C . Dry triethylamine (394 μl , 2.84 mmol) was added and the reaction was allowed to warm to room temperature slowly. After dilution with dichloromethane, the solution was washed with a saturated aqueous solution of sodium bicarbonate. Drying (Na_2SO_4), filtration and evaporation of the solvent afforded a crude residue. Column chromatography afforded the desired product a white foam (378 mg, 75.6%). MS (FAB) 880 ($m+1$).

The following compounds are prepared in an analogous manner:



INTERMEDIATES FOR EXAMPLES 1-15

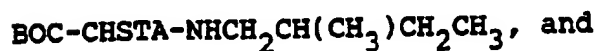
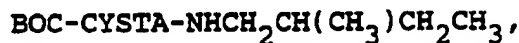
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66 BOC-STA (27.53 g, 0.1 mole, US Patent 4,397,786) and HOBT $\cdot\text{H}_2\text{O}$ (14.2 g, 0.105 mole) were dissolved in 40 ml DMF. 300 ml CH_2Cl_2 was added, and the mixture was cooled to 0° . A solution of DCC (21.66 g, 0.105 mole) in 50 ml CH_2Cl_2 was added, followed by S-2-methylbutylamine (12 ml, 0.1 mole). After stirring at 0° for two hours, the mixture was allowed to warm to 25° over 1.5 hours. The mixture was

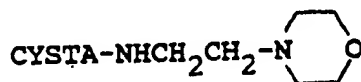
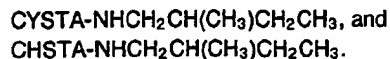
filtered, and the solvent was removed in vacuo. The residue was dissolved in EtOAc, which was washed with 1 N citric acid, brine, saturated NaHCO₃ solution, and brine. The organic phase was dried over MgSO₄, filtered, and stripped to a gum, 36.90 g. The gum was dissolved in Et₂O and treated with charcoal to remove colored impurities. The suspension was filtered and stripped to a gum, 35.2 g, which was suitable for use in the following procedure without further purification.

The following compounds are obtained in an analogous manner:

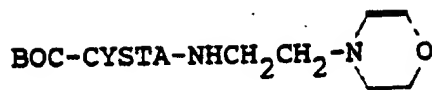


A solution of BOC-STA-NHCH₂CH(CH₃)CH₂CH₃ (15.4 g) in CH₂Cl₂ (300 ml) was treated with freshly prepared methanolic HCl (100 ml) and stirred 75 minutes at 25°. The resulting solution was evaporated and the residue partitioned between diethyl ether and 10% Na₂CO₃ (aq). The organic layer was dried over MgSO₄ and evaporated to give 9.9 g of a tacky, colorless solid which was suitable for use without further purification.

The following compounds are obtained in an analogous manner:

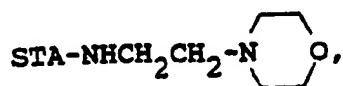


A solution of



5 (10 g) in CH_2Cl_2 (250 mL) was treated with methanolic HCl (250 mL) and stirred for 2 hours at 25° . The resulting solution was evaporated and the residue was treated with a saturated solution of ammonia in CH_2Cl_2 (300 mL). After 10 minutes of vigorous stirring, NH_4Cl was removed by filtration and the filtrate was evaporated to give the product as a solid.

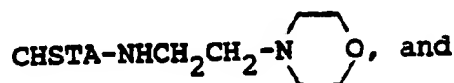
10 The following compounds are prepared in an analogous manner:



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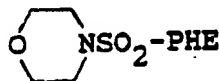
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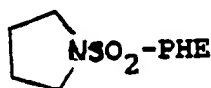
A solution of PHE (3.3 g) in 1 N NaOH (20 ml) was treated with a solution of N,N-dimethylsulfamyl chloride (2.3 ml) in THF (20 ml) and stirred vigorously at 25° for 3 hours. The reaction mixture was then treated with additional 1 N NaOH (20 ml) and N,N-dimethylsulfamyl chloride (2.3 ml) and stirred 3 hours further at 25° . Finally, 1 N NaOH (20 ml) and diethyl ether (80 ml) were added. The mixture was shaken and the aqueous layer was separated and acidified to pH 1 by addition of 1 N HCl (25 ml). Product was extracted into ethyl acetate, the solution was dried over MgSO_4 , and evaporated to give a gum which slowly solidifies (4.0 g). NMR δ (CDCl_3) 8.7 (br, 1H), 7.3 (m, 5H), 5.0 (d, 1H), 4.3 (m, 1H), 3.1 (AB of ABX, 2H), 2.6 (5, 6H).

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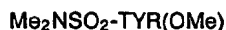


50 Prepared as above, substituting morpholinosulfamyl chloride (prepared according to the method of R. Wegler and K. Bodenbenner, *Annalen der Chemie*, 624, 25 (1959)) for N,N-dimethylsulfamyl chloride. Product is a solid, mp $151\text{-}153^\circ\text{C}$.

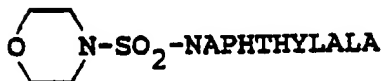
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Prepared as above, substituting pyrrolidinosulfamyl chloride for N,N-dimethylsulfamyl chloride. Product was isolated as its dicyclohexylamine salt, mp $172\text{-}174^\circ\text{C}$.

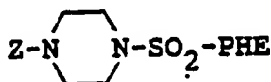


Prepared as above, substituting TYR(OMe) for PHE. Product was isolated as its dicyclohexylamine salt,
 5 mp 157-159° C.



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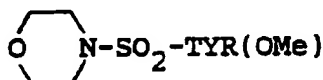
L-1-Naphthylalanine (860 mg) was converted to its tetra-n-butylammonium salt and dissolved in anhydrous THF (25 mL). This solution was treated with morpholinōsulfamyl chloride (370 mg) and stirred for 21 hours at room temperature in a stoppered flask. The resulting mixture was partitioned between ethyl acetate and 1N HCl. The organic layer was washed with 0.5 N NaOH and the basic aqueous layer was
 15 acidified to pH 2 with concentrated hydrochloric acid. The product was then extracted into a mixture of ethyl acetate and toluene, this solution was dried over magnesium sulfate and the dried solution was evaporated to give a crisp foam (440 mg). 100 MHz NMR (CDCl_3) δ 5.4 (broad doublet, SO_2NH). Excess naphthylalanine can be recovered for recycling by adjusting the first HCl extract to pH 5.5 and filtration of the
 20 resulting precipitate.



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L-Phenylalanine (1.65 g) was converted to its tetramethyl ammonium salt and dissolved in a mixture of anhydrous THF (50 mL) and anhydrous 2-propanol (12 mL). 4-Carbobenzyloxypiperazinosulfamyl chloride (1.59 g) was added and the reaction was stirred for 16 hours in a stoppered flask. The resulting suspension was evaporated and the residue was partitioned between dichloromethane and 1N HCl. The organic layer
 30 was washed with 1N HCl then extracted with 0.3 N NaOH (2x60 mL). The basic extracts were immediately acidified to pH 1 with concentrated HCl and extracted with ethyl acetate. This extract was dried over magnesium sulfate and evaporated to give the desired product as an off-white solid (1.35 g). 200 MHz NMR (CDCl_3 + DMSO-d_6) δ 6.2 (broad doublet, SO_2NH), 5.0 (s, $\text{Ph-CH}_2\text{-O}$).

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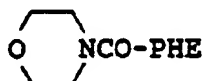
Prepared from the tetramethylammonium salt of TYR(OMe) and morpholinōsulfamyl chloride as above. 200 MHz NMR (CDCl_3 + DMSO-d_6) δ 6.0 (broad doublet, SO_2NH), 3.6 (s, OCH_3).



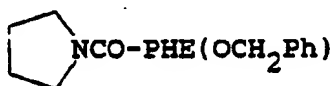
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A solution of morpholine (0.87 g), triethylamine (1.4 ml), and diethyl ether (100 ml) was added dropwise to a 17% solution of phosgene in toluene (15 g) at 0°. The mixture was warmed to 25° over one hour and solid removed by filtration. The filtrate was evaporated and redissolved in CH_2Cl_2 (25 ml). This solution was
 50 added to a solution of PHE(OCH_2Ph) (2.2 g), triethylamine (1.4 ml), and CH_2Cl_2 (50 ml). The reaction was kept at 25° for eighteen hours then washed with 0.5 N HCl. The organic layer was dried over MgSO_4 and evaporated. The residue was purified by flash chromatography on silica gel (CHCl_3) to give a gum which slowly solidifies (3.1 g). TLC R_f = 0.7 (silica gel, CHCl_3 -MeOH, 9:1).

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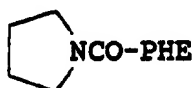
A solution of morpholinocarbamyl-PHE(OCH₂Ph) (3.0 g) in THF (100 ml) was treated with 10% Pd/C (0.25 g) under H₂ atmosphere (50 psi) for four hours. Catalyst was removed by filtration and the filtrate was evaporated to give a solid (2.3 g). TLC R_f = 0.1 (silica gel, CHCl₃-MeOH, 4:1).



10 Following the procedure for



15 above, pyrrolidine was substituted for morpholine.



Hydrogenolysis of the benzyl ester above using 10% Pd/C as catalyst, THF as solvent, and 50 psi H₂ atmosphere gives pyrrolidinocarbamyl-PHE.

MORPHOLINOACETIC ACID • HCl

30 A solution of ethyl bromoacetate (10 ml) in diethyl ether (150 ml) was treated dropwise with morpholine (16 ml). The resulting mixture was stirred two hours at 25°, filtered, and the filtrate was evaporated. The residue was distilled (Kugelrohr, 90-95°, 1 mm). The distillate (13.5 g) was heated at 90-95° in 6 N HCl (150 ml) for ninety minutes then evaporated to afford a crystalline mass. Trituration with 2-propanol and drying at 25 mm, 40° gives a colorless, crystalline solid (13 g), mp 169-171° C.



40 A mixture of morpholinoacetic acid • HCl (1.85 g), DCC (2.1 g), HOBT • H₂O (1.4 g), triethylamine (1.4 ml), and CH₂Cl₂ (100 ml) was stirred for ten minutes at 25° then treated with a solution of PHE(OCH₂Ph) (2.6 g) in CH₂Cl₂ (10 ml). After twenty-four hours at 25° the reaction mixture was filtered and the filtrate was washed with 5% aqueous Na₂CO₃ (75 ml), dried over MgSO₄, and evaporated. The major product was isolated by flash chromatography on silica gel, eluting with CHCl₃-ethyl acetate (98:2). MS (FAB) 383 (m + 1).

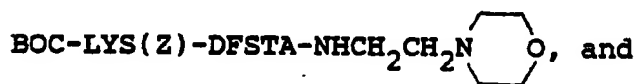


50 Hydrogenolysis of morpholinoacetyl-PHE(OCH₂Ph) was performed in the same manner as for morpholinocarbamyl-PHE(OCH₂Ph) to give this compound. NMR δ 8.8 (br, 1H), 7.6 (d, 1H), 7.2 (m, 5H), 4.7 (q, 1H), 3.6 (t, 4H), 3.1 (m, 4H), 2.5 (t, 4H).

BOC-LYS(Z)-STA-NHCH₂CH(CH₃)CH₂CH₃

BOC-LYS(Z) (1.98 g), STA-NHCH₂CH(CH₃)CH₂CH₃ (1.3 g), HOBT·H₂O (0.72 g), were mixed together in DMF (15 ml) and cooled to 0°. DCC (1.1 g) was added, and the mixture was allowed to warm slowly to 25° and then stir for seventy-two hours. The mixture was filtered, and the filtrate was extracted with EtOAc and water. The organic phase was washed with water, sodium bicarbonate solution, and brine. The organic phase was dried over sodium sulfate, filtered, and evaporated. The residue was eluted from silica gel with 1:1 EtOAc/hexane to give 2.7 g of product.

The following compounds are prepared in an analogous manner:



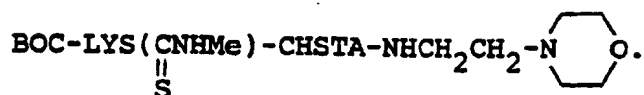
A solution of BOC-LYS(Z)-STA-NHCH₂CH(CH₃)CH₂CH₃ (5.1 g) in MeOH (100 ml) was treated with 20% Pd/C (1.0 g) under H₂ atmosphere (50 psi) for six hours at 25°. Catalyst was removed by filtration and the filtrate was evaporated to a solid. This solid was dissolved in a mixture of CHCl₃ (40 ml) and THF (80 ml) and treated with methyl isothiocyanate (0.62 g). The resulting solution was stirred at 25° overnight and evaporated. The major product was isolated by flash chromatography on silica gel, eluting with CHCl₃-MeOH (98:2) to afford the desired product (4.1 g). MS (FAB) 546 (m + 1).

The following compounds are prepared in an analogous manner:





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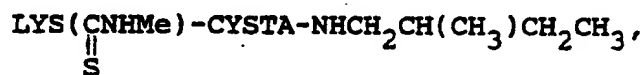
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A solution of the above BOC-protected dipeptide (2 g) in CH_2Cl_2 (40 ml) was treated with methanolic HCl (20 ml), stirring at 25° for one hour. The reaction mixture was evaporated and the residue was partitioned between CH_2Cl_2 (50 ml) and 10% aqueous Na_2CO_3 (25 ml). The organic layer was dried over MgSO_4 and evaporated to a gum. TLC $R_f = 0.1$ (silica gel, CHCl_3 -MeOH, 9:1).

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The following compounds are prepared in an analogous manner:

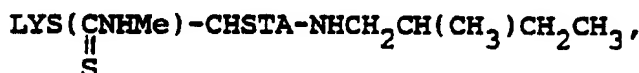
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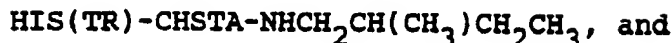


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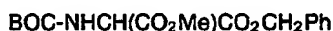


A solution of Z-HIS(TR)-STA-NHCH₂CH(CH₃)CH₂CH₃ (5.4 g) in MeOH (200 ml) was treated with 20% Pd/C (0.5 g) under H₂ atmosphere (50 psi) at 25° . After five hours the catalyst was removed by filtration and the filtrate was evaporated to give a gum (4.4 g). TLC $R_f = 0.2$ (silica gel, CHCl_3 -MeOH, 9:1).

The following compounds are prepared in an analogous manner:



Methyl, benzyl isonitroso malonate was prepared from methyl, benzyl malonate (obtained from Aldrich Chemical Corp.) by the procedure described in Organic Synthesis, Col. Vol. V, p. 373. The crude product thus obtained was reduced to the title compound by the procedure described in the Journal of the American Chemical Society, Vol. 75, p. 1970, April 20, 1953. Crude product was used without further purification or analyses in the following step.



$\text{H}_2\text{NCH(CO}_2\text{Me)CO}_2\text{CH}_2\text{Ph}$ (94 g) was dissolved in ethyl ether (750 ml) and cooled to 5°. Di-*t*-butyldicarbonate (91.7 g) was added and the mixture was held at 4° overnight. The mixture was stripped to an orange oil (135 g). This oil was chromatographed on silica gel, eluting with hexane-ethyl acetate (85:15). The major product was recovered as an oil which solidified upon standing (67 g). MS (FAB) 324 (*m* + 1).

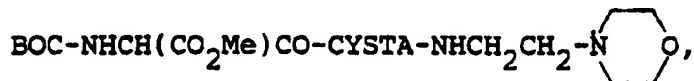


$\text{BOC-NHCH(CO}_2\text{Me)CO}_2\text{CH}_2\text{Ph}$ (16.2 g) was dissolved in MeOH (250 ml), to which was added 20% Pd/C (0.66 g). The suspension was purged with H₂ for 1.5 hours, filtered, and stripped at 30° in vacuo, giving a syrup (12.5 g) which was kept at 4° until use in the following step.



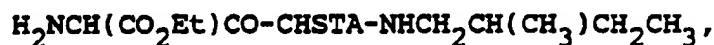
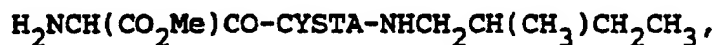
$\text{BOC-NHCH(CO}_2\text{Me)CO}_2\text{H}$ (12.5 g) was dissolved in CH₂Cl₂ (340 ml) and cooled to -3°. A solution of HOBT·H₂O (7.0 g) in DMF (15 ml) was added, followed by a cold solution of DCC (10.6 g) in CH₂Cl₂ (50 ml). A cold solution of STA-NHCH₂CH(CH₃)CH₂CH₃ (11.3 g) in CH₂Cl₂ (60 ml) was then added and the mixture was stored at 4° overnight. The mixture was filtered and the filtrate was washed consecutively with 1 N citric acid, brine, saturated aqueous NaHCO₃, and brine. The organic phase was dried over MgSO₄ and stripped to a glass (23.3 g). Chromatography on silica gel, eluting with CHCl₃-MeOH (98:2) gives the purified product as a foam (13.9 g). MS (FAB) 460 (*m* + 1).

The following compounds are prepared in an analogous manner:



BOC-NHCH(CO₂Me)CO-STA-NHCH₂CH(CH₃)CH₂CH₃ (18.6 g) was dissolved in CH₂Cl₂ (300 ml), to which was added trifluoroacetic acid (50 ml). After stirring two hours, the mixture was stripped to a syrup which was taken up in ethyl ether-ethyl acetate (1:1). This solution was charged with saturated aqueous NaHCO₃ (50 ml), followed by agitation. Additional solid NaHCO₃ was added until the mixture became saturated. The organic phase was washed with brine, dried over MgSO₄ and stripped to a yellow foam (10.5 g) which was suitable for use in subsequent steps (Example 8) without further purification. MS (FAB) 360 (m + 1).

The following compounds are prepared in an analogous manner:





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A mixture of BOC-ALG (1.76 g), HOBT·H₂O (1.16 g) and DMF (20 mL) was stirred in an ice bath and treated with STA-NHCH₂CH(CH₃)CH₂CH₃ (2.0 g) and DCC (1.79 g). The mixture was stirred in an ice bath for 3 hours and then overnight at room temperature. After filtering, the filtrate was concentrated under high vacuum. The residue was taken up in EtOAc and washed with 1N citric acid, brine, saturated NaHCO₃, and brine. After drying over Na₂SO₄, the solution was concentrated to yield an orange solid which was purified by flash chromatography (MeOH/CHCl₃ 2:98) to yield BOC-ALG-STA-NHCH₂CH(CH₃)CH₂CH₃ (2.1 g) as a white foam. MS (FAB) 442 (m + 1).

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The following compounds are obtained in an analogous manner:

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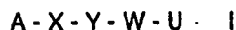
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ALG was prepared according to the procedure described in the Journal of the American Chemical Society, Vol. 109, pp. 4649-4659, 1987. A solution of ALG (16 g) in a mixture of dioxane (150 mL) and 2N NaOH (70 mL) was treated with di-*t*-butyldicarbonate (34 g). The mixture was stirred overnight, basified to pH = 8.5 with 2N NaOH, diluted with water and extracted with ether. The aqueous solution was acidified

with citric acid and extracted twice with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4 and concentrated to yield BOC-ALG as a solid. MS (Cl , CH_4) 216 ($m+1$).

6 Claims

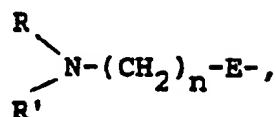
1. A peptide of the formula



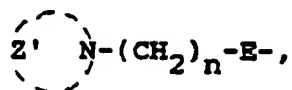
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or a pharmaceutically acceptable acid addition salt thereof wherein A is

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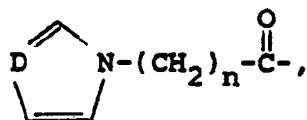
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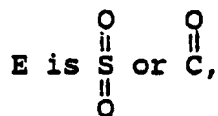
or

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wherein R and R' are each independently hydrogen, benzyl or lower alkyl;

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is a saturated ring of from 1 to 5 carbon atoms

wherein Z' is CH_2 , O, S, or NR,

n is an integer of from 0 to 3; and

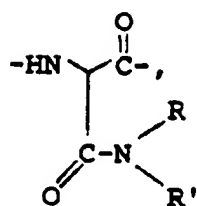
50 D is N, S, O, or CH;

X is PHE, HOMOPHE, TYR, TYR(OMe), CYCLOHEXYLALA, LEU, NAPHTHYLALA, TRP, HIS, or (NMe)PHE;

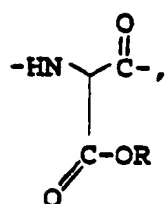
Y is GLN, HIS, LEU, PGY, MET, TZA, ALG, PPG, CPM, EMG, BYG, NIA,

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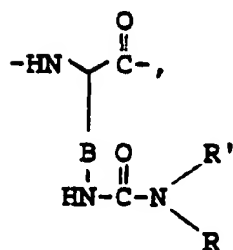


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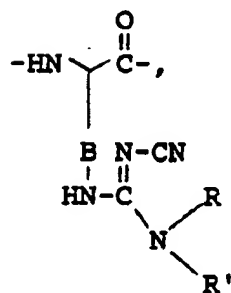
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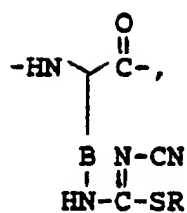
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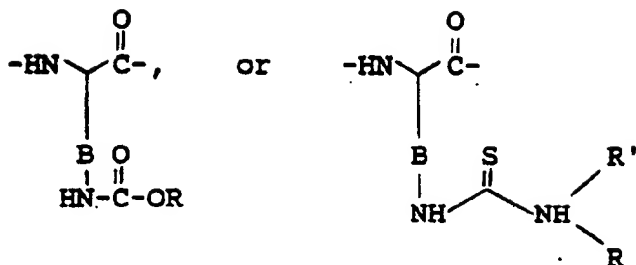
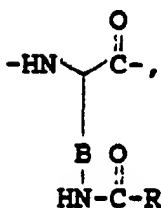
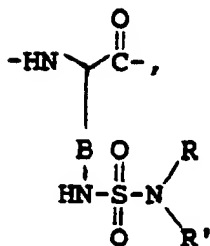
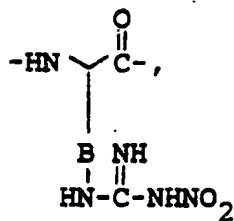
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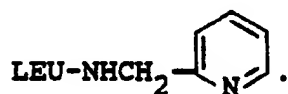
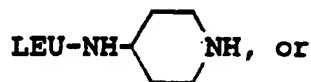
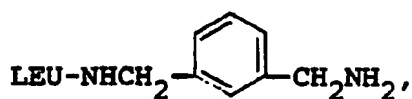
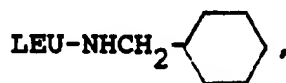
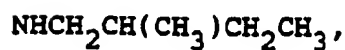
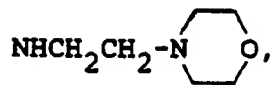
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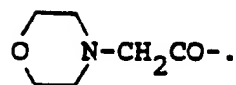
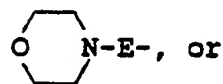
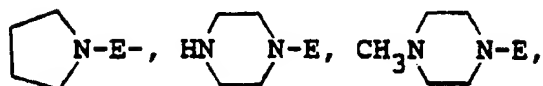
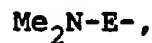
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40 wherein B is a carbon chain of from 3 to 6 carbon atoms which is saturated, unsaturated, or acetylenic;
 R and R' are each independently hydrogen, benzyl or lower alkyl;
 W is STA, CYSTA, or PHSTA, CHSTA, ASTA, ACYS, DFKSTA, DFKCYS, DFKCHS; and
 U is

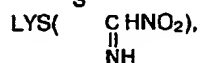
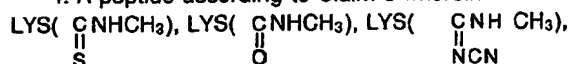


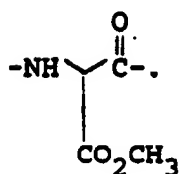
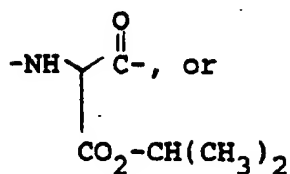
2. A peptide according to Claim 1 wherein A is



3. A peptide according to Claim 2 wherein X is PHE, NAPHTHYLALA or TYR(OMe).

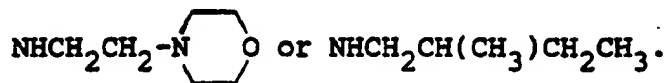
4. A peptide according to Claim 3 wherein Y is HIS, TZA, PGY, ALG,



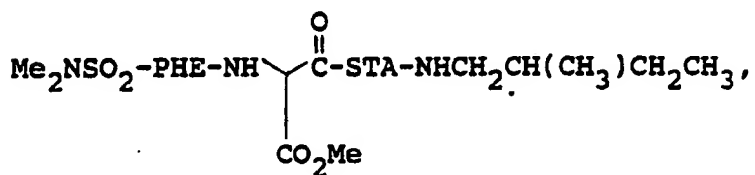
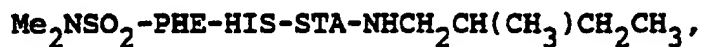


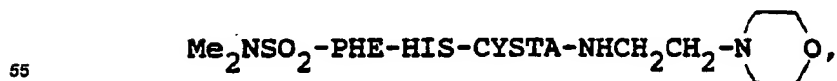
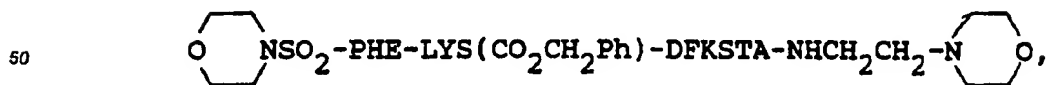
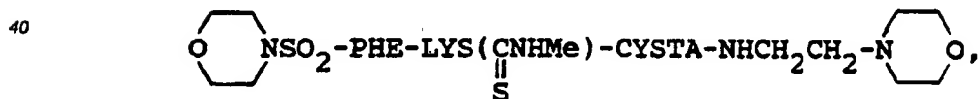
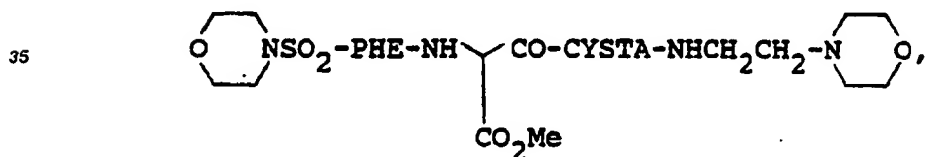
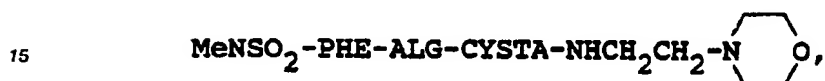
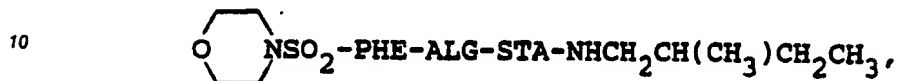
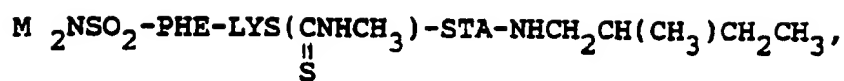
5. A peptide according to Claim 4 wherein W is STA, CYSTA, CHSTA, DFKCYS, OR DFKSTA.

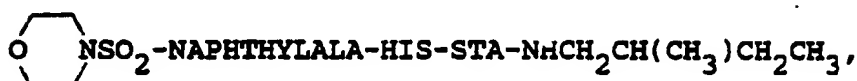
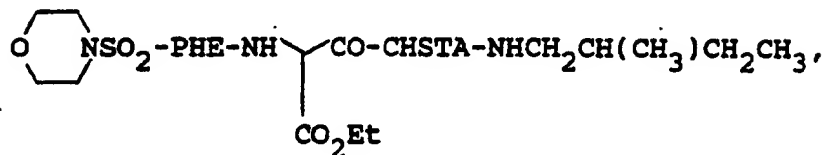
6. A peptide according to Claim 5 wherein U is



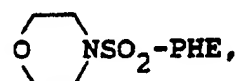
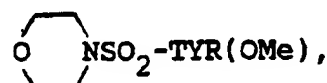
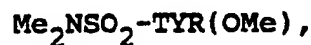
7. A peptide according to Claim 1 wherein the peptide is a member selected from the group consisting of:

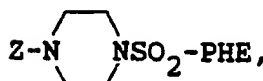
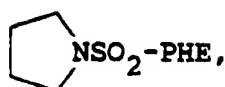






8. A compound named





10 and the dicyclohexylamine salts thereof.

9. A pharmaceutical composition comprising a renin-inhibitory effective amount of a peptide as claimed in Claim 1 together with a pharmaceutically acceptable carrier.

10. A method of treating renin-associated hypertension which comprises administering to a mammal a pharmaceutical composition as claimed in Claim 9.

15 11. A pharmaceutical composition comprising a hyperaldosteronism-inhibitory effective amount of a peptide as claimed in Claim 1 together with a pharmaceutically acceptable carrier.

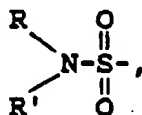
12. A method of treating hyperaldosteronism which comprises administering to a mammal a pharmaceutical composition as claimed in Claim 11.

20 13. A pharmaceutical composition comprising an amount effective for treating congestive heart failure of a peptide as claimed in Claim 1 together with a pharmaceutically acceptable carrier.

14. A method of treating congestive heart failure which comprises administering to a mammal a pharmaceutical composition as claimed in Claim 13.

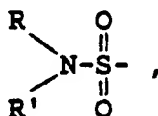
25 15. A method of determining the presence of renin-associated hypertension in a patient, comprising administering to such a patient, at a hypotensive dosage level and as a single dose, a peptide according to Claim 1, followed by monitoring of said patient's blood pressure.

16. A process for the preparation of compounds of Claim 1 wherein A is



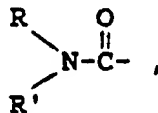
35 which comprises reacting at least two equivalents of a sulfamyl chloride with at least one equivalent of amino acid as in X, an inorganic aqueous base and a water-miscible organic solvent to give a sulfamyl-amino acid, followed by coupling of the latter to the -Y-W-U fragment and if desired, converting to a pharmaceutically acceptable acid addition salt thereof by known means.

17. A process for the preparation of compounds of Claim 1 wherein A is



45 which comprises reacting a sulfamyl chloride with the tetra-alkylammonium salt of an amino acid as in X, in an anhydrous organic solvent to give a sulfamyl-amino acid, followed by coupling of the latter to the -Y-W-U fragment and if desired, converting to a pharmaceutically acceptable acid addition salt thereof by known means.

50 18. A process for the preparation of compounds of Claim 1 wherein A is



55 which comprises reacting at least one equivalent of a carbamyl chloride with at least one equivalent of an

amino acid benzyl ester as in X, an organic base and an aprotic organic solvent to produce a carbamyl amino acid benzyl ester, hydrogenolysis in the presence of a noble metal catalyst to give a carbamyl amino acid, and subsequent coupling of the latter to the -Y-W-U fragment and if desired, converting to a pharmaceutically acceptable acid addition salt thereof by known means.

5 19. Use of a compound of formula I for the preparation of a pharmaceutical composition for the treatment according to Claims 10, 12 and 14.

20. Use of a compound of formula I for the preparation of a diagnostic composition for determining the presence of renin-associated hypertension according to Claim 15.

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